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LAY PERSPECTIVES ON RISKS OF COMMON DISEASES AND SECONDARY FINDINGS OF GENOME SEQUENCING

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ACADEMIC DISSERTATION

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ABSTRACT

Medical genetics and genetic technology have evolved rapidly during the past decades. Whole genome and exome sequencing are increasingly common in research settings, and they are likely to become more common in clinical settings as well. Efficient use of genomic information requires understanding of how lay people perceive hereditary risks and how they interpret genomic risk information. This study explored lay perspectives on risks of common diseases and secondary findings of genome sequencing.

This study consisted of two quantitative and two qualitative sub-studies. Quantitative sub-study I (N=6258) examined whether family history of disease was related to perceived personal risk of diabetes, cardiovascular disease, cancer, and depression. Quantitative sub-study II (N=909) used structural equation modelling to examine relationships of perceived risks of diabetes and cardiovascular disease, health action self-efficacy and outcome beliefs, and risk indicators during a five-year follow-up. The study included people with a high or low to moderate diabetes risk status, who received biomarker feedback after baseline assessment. Participants of the quantitative sub-studies were from the FINRISK 2002 and 2007 health examination and survey studies, conducted by the Finnish National Institute for Health and Welfare.

The qualitative inquiry (sub-studies III and IV) used a hypothetical scenario to examine lay perspectives on genetic secondary findings. Participants imagined themselves in a situation of receiving, via letter, a secondary finding predisposing to heritable cancer (Lynch syndrome or Li–Fraumeni syndrome) or heart condition (long QT syndrome or familial hypercholesterolemia). Participants wrote down their immediate reactions (N=29) and discussed the topic later in focus groups (N=23). The transcribed data were analysed through inductive thematic analysis. Sub-study III explored concerns and needs related to secondary findings in general, whereas sub-study IV looked at how type of disease shapes these perspectives.

Family history was related to perceived risk of common diseases independently of sociodemographics, health behaviour, body weight, and depressive symptoms. This association was weaker for depression compared to somatic diseases. (Sub-study I.) In the longitudinal setting, perceived risk or outcome beliefs did not predict changes in physical activity, body weight, or glucose tolerance. In contrast, those with higher baseline risk indicators tended to perceive higher disease risks after five years. Those with a high baseline self-efficacy increased their weekly physical activity. Results were similar among participants with a high risk for diabetes and those with a low or moderate risk, although those at high risk tended to underestimate their risk. (Sub-study II.)

Results of the qualitative inquiry showed that despite a positive attitude towards receiving secondary findings, people were worried whether relevant counselling and preventive care would be accessible for individuals and families. For the analysis concerning general perspectives on secondary findings, identified main themes were *immediate shock, dealing with worry and heightened risk, fear of being left alone to deal with secondary findings, disclosing to family* and *support needs*. Support needs included *information*, *access to care*, and *empathetic communication*. (Sub-study III.) Type of disease contributed to how these worries were emphasized. Main themes concerning types of diseases were *familiarity*, *severity in terms of lived experience*, *cancer vs. heart disease*, *somatic vs. psychiatric disease*, *access to treatment*, *stigma*, and *responsibility*. (Sub-study IV.)

People tend to view their disease risks optimistically, but risk perceptions of common diseases reflect actual risk indicators. Perceived risk of disease or individualized biomarker feedback alone, however, are unlikely to result in sustained changes in daily health behaviour. Increasingly individualized risk communication practices need to also direct attention to counselling and supporting self-efficacy. Lay illness representations need to be taken into account in risk communication, as previous understandings of diseases shape how people process new risk information. When reporting genomic results, preventive treatment paths for individuals and families need to be planned and communicated appropriately.

TIIVISTELMÄ

Lääketieteellinen genetiikka ja geeniteknologia ovat kehittyneet nopeasti viime vuosikymmeninä. Koko genomin tai eksomin laajuiset analyysit ovat yleistyneet geenitutkimuksessa ja ne yleistynevät tulevaisuudessa myös kliinisessä työssä. Geenitiedon paras mahdollinen hyödyntäminen edellyttää tietoa myös siitä, kuinka maallikot hahmottavat perinnöllisiä riskejä ja tulkitsevat genomitutkimuksista saatavaa riskitietoa. Tässä tutkimuksessa tutkittiin maallikoiden näkökulmia monitekijäisten kansantautien riskeihin ja genomitutkimusten sekundaarilöydöksiin.

Tutkimus koostui kahdesta määrällisestä ja kahdesta laadullisesta osatutkimuksesta. Määrällinen osatutkimus I (N=6258) selvitti, onko sukuhistoria yhteydessä koettuun henkilökohtaiseen sairastumisriskiin diabeteksen, sydän- ja verisuonitautien, syövän ja masennuksen kohdalla. Määrällinen osatutkimus II (N=909) tutki rakenneyhtälömallinnuksen avulla yhteyksiä diabeteksen sekä sydän- ja verisuonitautien koetun sairastumisriskin, elintapamuutoksiin liittyvän pystyvyyskokemuksen ja tulosodotusten sekä riskitekijöiden välillä viiden vuoden seurannassa. Osalla tutkimuksen osallistujista oli korkea diabetesriski, osalla matala tai keskitasoa. Määrällisissä tutkimuksissa käytettiin Terveyden ja hyvinvoinnin laitoksen keräämiä FINRISKI 2002 ja 2007 kysely- ja terveystutkimusaineistoja.

Laadullisessa osassa (osatutkimukset III ja IV) tutkittiin maallikoiden näkökulmia sekundaarilöydöksiin eläytymismenetelmän avulla. Osallistujat eläytyivät kuvitteelliseen tilanteeseen, jossa saivat kirjeellä tiedon sekundaarilöydöksestä, joka altistaa perinnölliselle syövälle (Lynch oireyhtymä tai Li–Fraumeni oireyhtymä) tai sydänsairaudelle (pitkä QT-aika -oireyhtymä tai familiaalinen hyperkolesterolemia). Osallistujat kirjoittivat ensireaktionsa (N=29) ja keskustelivat aiheesta myöhemmin fokusryhmissä (N=23). Litteroitu aineisto analysoitiin induktiivisen temaattisen analyysin menetelmällä. Osatutkimus III tarkasteli sekundaarilöydöksiin liittyviä huolia ja tarpeita yleisellä tasolla, ja osatutkimus IV selvitti, kuinka kyseessä olevan taudin luonne muovasi näitä näkökulmia.

Sukuhistoria oli yhteydessä kansantautien koettuun riskiin riippumatta sosioekonomisista tekijöistä, elintavoista, kehon painosta tai masennusoireista. Masennuksen kohdalla yhteys oli heikompi kuin somaattisten sairauksien kohdalla. (Osatutkimus I). Pitkittäisasetelmassa koettu riski ja tulosodotukset eivät ennustaneet muutoksia liikunnassa, kehon painossa tai glukoosinsietokyvyssä. Päinvastoin lähtötilanteen kohonneet riskitekijät ennustivat korkeampia koettuja riskejä viiden vuoden päästä. Ne, joiden pystyvyyskokemus oli lähtötilanteessa korkea, lisäsivät liikuntaa viiden vuoden seurannan aikana. Tulokset olivat samanlaiset osallistujilla, joilla oli lähtötilanteessa korkea diabetesriski ja heillä, joiden riski oli matala tai

keskitasoa. Korkeassa riskissä olevat kuitenkin aliarvioivat riskinsä. (Osatutkimus II.)

Laadullisen osan tulokset osoittivat, että huolimatta myönteisestä suhtautumisesta sekundaarilöydösten vastaanottamiseen, osallistujat olivat huolissaan aiheeseen liittyvän neuvonnan ja ennaltaehkäisevän hoidon saatavuudesta yksilöille ja perheille. Sekundaarilöydöksiin liittyviä yleisiä näkökulmia tarkastelevan analyysin keskeiset teemat olivat *välitön shokki*, *huolen ja riskin käsittely*, *pelko yksin jäämisestä sekundaarilöydöksen kanssa*, *perheelle kertominen* ja *tuen tarpeet*. Tuen tarpeisiin kuului *tieto*, *hoitoon pääseminen* ja *empaattinen vuorovaikutus*. (Osatutkimus III.) Sairauden luonne toi osansa siihen, kuinka näitä huolia painotettiin. Sairauden luonnetta koskevat keskeiset teemat olivat *tuttuus*, *vakavuus elettynä kokemuksena*, *syöpä vs. sydänsairaus*, *somaattinen vs. psykiatrinen sairaus*, *hoitoon pääseminen*, *sosiaalinen leima* ja *vastuu*. (Osatutkimus IV.)

Ihmiset arvioivat riskejään optimistisesti, mutta kokemukset kansantautien riskeistä heijastelevat tosiasiallisia riskitekijöitä. Koettu riski tai terveystarkastuspalautteen saaminen ei kuitenkaan yksinään todennäköisesti johda pysyviin elintapamuutoksiin. Yhä yksilöllistetymmässä riskiviestinnässä tulee huomioida myös neuvonnan ja pystyvyyskokemusten merkitys. Maallikoiden käsitykset sairauksista on huomioitava riskiviestinnässä, sillä ne muovaavat uuden riskitiedon käsittelyä. Kun annetaan genomitutkimuksista saatavaa riskitietoa, ennalta ehkäisevät hoitopolut yksilöille ja perheille on suunniteltava ja selvitettävä riskitiedon saajalle asianmukaisesti.

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Helsinki, May 2019

Marleena Vornanen

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Vornanen, M., Konttinen, H., Kääriäinen, H., Männistö, S., Salomaa, V., Perola, M., and Haukkala, A. (2016). Family history and perceived risk of diabetes, cardiovascular disease, cancer, and depression. *Preventive Medicine* 90, 177–183. https://doi.org/10.1016/j.ypmed.2016.06.027

II Vornanen, M., Konttinen, H., Peltonen, M., and Haukkala, A. (20xx). Diabetes and cardiovascular disease risk perception and risk indicators: A five-year follow-up. Submitted.

III Vornanen, M., Aktan-Collan, K., Hallowell, N., Konttinen, H., Kääriäinen, H., and Haukkala, A. (2018). "I would like to discuss it further with an expert": a focus group study of Finnish adults' perspectives on genetic secondary findings. *Journal of Community Genetics* 1–10. https://doi.org/10.1007/s12687-018-0356-6

IV Vornanen, M., Aktan-Collan, K., Hallowell, N., Konttinen, H., and Haukkala, A. (2018). Lay perspectives on receiving different types of genomic secondary findings: a qualitative vignette study. *Journal of Genetic Counseling* 00: 1–12. https://doi.org/10.1007/s10897-018-0288-7

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

ACMG	American College of Medical Genetics and Genomics
BMI	body mass index
CES-D	Center for Epidemiological Studies Depression Scale
CFI	Comparative Fit Index
CSM	Common Sense Model of illness represenations
CVD	cardiovascular disease
DF	degrees of freedom
DILGOM	Dietary, Lifestyle and Genetic Determinants of Obesity and Metabolic Syndrome Study
FH	familial hypercholesterolemia
FINRISK	The National Cardiovascular Risk Factor Survey
HAPA	Health Action Process Approach
LFS	Li–Fraumeni syndrome
LS	Lynch syndrome
LQTS	long QT syndrome
RMSEA	Root Mean Square Error of Approximation
SD	standard deviation
SEM	structural equation modelling
TLI	Tucker-Lewis Index

1 INTRODUCTION

Risk communication is a common health promotion strategy. Risk factors of common chronic diseases are frequently discussed in the media, and also the healthcare informs patients about risks that may be related to their family history, lifestyle, or physiological measures. Common diseases like type 2 diabetes, cardiovascular diseases (CVD), and cancers are usually multifactorial; their risk factors include health behaviour, environmental exposures, and genetic predisposition. Currently, there is a trend of personalized medicine, which hopes to provide more individualised risk information and treatment (Katsios & Roukos, 2010). An essential component of personalised medicine is taking into account individual genetic predispositions. Whole genome sequencing means mapping an individual's entire DNA sequence at once, whereas whole exome sequencing maps the protein coding region of the genome. With these techniques it is possible to analyse individuals' ancestry but also several types of health related information: polygenic risk scores for multifactorial diseases, pharmacogenetic variants that indicate individual harms or benefits of certain medications, carrier status of recessive diseases, and single variants that indicate high risks for diseases. Single variants that indicate disease risks are commonly called 'secondary findings' if they were not the initial target of the investigation. A lot of expert discussion has been going on around how to handle various types of secondary findings.

While clinical genetic testing for single gene disorders such as Huntington's disease started in the late 1980s (Meissen et al., 1988), whole genome or exome sequencing has lately become more and more common in research settings and is likely to get integrated into clinical care in the near future. Costs of whole genome sequencing have decreased dramatically: sequencing the first human genome cost approximately 500–1000 millions of US dollars during a 13-year project, whereas a few years ago (2016) whole genome sequencing generally cost less than 1000 US dollars (National Human Genome Research Institute, n.d.). Hence, it is getting more and more practical to use whole genome or exome sequencing instead of single genetic tests. To use genomic information for better health of individuals and populations, we also need to understand how lay people understand and use hereditary risk information. The European Society of Human Genetics states that public perspectives need to be taken into account when integrating genome sequencing into healthcare (van El et al., 2013).

This study examines lay perspectives on hereditary risk information from two angles. First, the study uses nationally representative health examination and survey data to examine how health behaviour and family history of common diseases are related to personal disease risk perceptions. Second, the study uses a qualitative approach to explore lay people's perspectives on

receiving secondary findings from genome sequencing. This study was conducted as part of a larger research project funded by the Academy of Finland (project number: 275033), which examined public understandings of genomics from various perspectives. The topic is timely as several countries, including Finland, have established national strategies for handling and taking use of genetic data (Ministry of Social Affairs and Health, 2015). The Finnish legislation around biobanks was recently updated (FINLEX ®, 2012). A special genome law is currently being prepared.

1.1 GOALS OF PERSONALISED AND PREVENTIVE MEDICINE

Personalised medicine aims to customize risk calculations and treatments individually (Katsios & Roukos, 2010). Recent decades' advances in the field of genomics have particularly promoted this perspective. The trend of *preventive* medicine, however, has been prominent for a longer time. The idea is to allocate resources to preventing illness instead of only treating it, so that human suffering and treatment costs could be reduced. Research around risks for CVD, in particular, has a numerous decades long tradition in Finland (Puska, Vartiainen, Laatikainen, Jousilahti, & Paavola, 2009) and other countries (Dawber, Meadors, & Moore Jr, 1951). Between years 2000–2010 there was a national diabetes prevention program in Finland (Saaristo et al., 2007; Wikström et al., 2015). Despite efforts in risk communication to populations and individuals, chronic non-communicable diseases – including type 2 diabetes, CVD, and cancers – are extremely common worldwide (Lozano et al., 2012), and their prevalence is increasing. For example, 10.4% of adults worldwide are expected to have diabetes by 2040 (Ogurtsova et al., 2017). Preventive methods include sustained changes in weight, diet, and physical activity (Lindström et al., 2006).

In addition to chronic somatic diseases, depression and other mental disorders cause a significant disease burden. Depressive disorders are a leading cause of years lived with disability (Ferrari et al., 2013), and it is estimated that 4.4% of the global population are currently living with depression (WHO, 2017). In Finland, depression is a growing public health problem (Markkula et al., 2015). Adverse social circumstances are a major risk factor (Dunn et al., 2015). Similarly to common somatic diseases, genetic predisposition has a clear role in vulnerability to depression (Dunn et al., 2015; Sullivan, Neale, & Kendler, 2000), and health behaviours such as physical activity have preventive potential (Teychenne, Ball, & Salmon, 2008). However, risk communication practices for psychiatric disorders are considerably more cautious compared to somatic diseases. Reasons behind this include that their etiology is very complex, and that such risk information

is seen as potentially stigmatizing (Bunnik, Schermer, & Janssens, 2012; Kostick, Brannan, Pereira, & Lázaro-Muñoz, 2018). Many experts favour communicating psychiatric genetic risks but wish to avoid causing harmful distress to people who already have psychiatric problems (Kostick et al., 2018).

Perspectives of preventive and personalised medicine tend to be combined. Individual disease risks are often at focus also without genetic testing: for example, there are easily accessible online risk assessment tools, which calculate individuals' risks based on multiple risk factors (National Institute for Health and Welfare, 2018). One way, for health professionals and lay people alike, to assess individual disease risk is to look at family history. Family pedigrees are used in medical genetics when examining hereditary diseases that are caused by single genetic variants, but family history also predicts individual's risk for multifactorial diseases (Guttmacher, Collins, & Carmona, 2004; Yoon et al., 2002). Particularly early onset indicates familiality of common diseases like CVD (Jousilahti, Puska, Vartiainen, Pekkanen, & Tuomilehto, 1996), diabetes (Almgren et al., 2011), cancer (Risch, 2001), and depression (Levinson, 2006). Family history combines risk information from genetics and lifestyle, since health behaviour is often shared in families. For healthcare professionals, family history is easy to assess, since no genetic tests are needed. For lay people, family history is a meaningful way of evaluating genetic risk, since lay people tend to understand genetics in terms of traits and diseases that 'run in families' (Condit, 2010b), instead of a more detailed understanding of how genes function.

It is also known that individuals' expectations affect how they interpret new risk information (Renner, 2004). Family history is likely to shape people's expectations of genetic test results. For example, one study found that receipt of genetic test results concerning diabetes risk changed risk perceptions only among people who had diabetes in their family (Shiloh et al., 2015). This is why family history of disease needs to be taken into account when communicating genetic risks. Polygenic risk scores complement risk information indicated by family history, which continues to be an important tool for assessing risks for common multifactorial diseases (Aiyar et al., 2014).

When using genome sequencing, for example to calculate polygenic risk scores, there is also the possibility to detect secondary findings. If a person's genome or exome is sequenced for a specific reason, should also other health related variants be searched for and reported to the individual? Secondary findings usually refer to single variants that are known to implicate high risk for heritable diseases. Sometimes such findings are also called incidental findings. However, this term has been critized, since they are not, in fact, incidental or accidental, but finding them requires active analytical effort (Shkedi-Rafid, Dheensa, Crawford, Fenwick, & Lucassen, 2014). Often the term 'secondary findings' is preferred for this reason.

Experts have intensely debated on the issue of secondary findings. The discussion has included several points of views: *whether* and *what* to report (Christenhusz, Devriendt, & Dierickx, 2013), how to deal with *uncertainties* of

genetic risk information (Newson, Leonard, Hall, & Gaff, 2016), how to obtain valid *informed consent* (Appelbaum et al., 2014; Berg, Khoury, & Evans, 2011; Bunnik et al., 2012; Mackley, Fletcher, Parker, Watkins, & Ormondroyd, 2016), and how to balance between *clinical and research ethics principles* (Hallowell, Hall, Alberg, & Zimmern, 2015). Today, the overall consensus is that scientifically robust, analytically valid, clinically actionable findings should be reported to patients and research participants who have consented to receive them (Knoppers, Zawati, & Sénécal, 2015; Wolf, 2013). There are no guidelines for reporting variants of unknown significance (Solomon et al., 2017), which could potentially evoke distress but would not lead to any medical interventions. As a response to *what* to report, the American College of Medical Genetics and Genomics (ACMG) has provided a list of 59 genes whose pathogenic variants should be reported to patients who consented to receive them in clinical settings (Kalia et al., 2016). This list includes genes that are related to 'actionable diseases', which means there are preventive methods available if the risk is known. The listed variants predispose to, for instance, certain cancers or cardiovascular conditions, whose preventive methods include surveillance, surgery, and medication.

It has been pointed out that research settings and clinical practice are guided by, to some degree, different ethical principles (Hallowell et al., 2015). One important difference is that clinical practice is guided primarily by ethics of care, whereas participation in research is, in principle, supposed to be altruistic: the participant is not supposed to seek care or other benefits through participating research. This poses challenges, since genetic research and clinical practice tend to be embedded in practice, and it is not always clear, which ethical principles should be emphasized in different circumstances. Possibilities to provide counselling before consenting to receive secondary findings, for instance, are better in clinical settings where patients have face to face contact with healthcare professionals, compared to research settings where the same is not always possible. To handle secondary findings and other types of genomic information in ways that eventually promote health, we also need to understand how lay people understand and use such information.

1.2 EXPERT AND LAY PERSPECTIVES ON GENOMICS

Professionals and lay people tend to have somewhat different perspectives on genetics. Medical professionals may primarily think of the genome as a source of health information that can help diagnosis and risk assessment, but lay people interpret genetic information from the perspective of their whole life, identity, and social relations (Rehmann-Sutter & Mahr, 2016). Moreover, medical professionals have more detailed information on specific diseases and their treatment possibilities, whereas lay people make sense of different

diseases through more general dimensions (Leventhal, Meyer, & Nerenz, 1980). Lay illness representations of diseases emphasize not only their symptoms and treatability, but also their consequences for one's individual and social life as a whole. Hence, health professionals and lay people may see different kinds of potential to use and misuse genetic risk informaton of various types of diseases. Lay perspectives need to be taken into account when decisions are made about how genomic information is used in research and healthcare practices, in order to achieve acceptable practices that promote health.

This thesis aims to shed light on the lay perspective on genetic risks, while acknowledging that the 'professional' and 'lay' divide is artificial and not mutually exclusive. Health professionals may be in the position of a patient or research participant similarly as anyone else; and also lay people have scientific knowledge about diseases and their prevention. Lay and professional understandings of diseases overlap in many ways (Damman & Timmermans, 2012). In general, however, professionals have the possibility to take into account more detailed scientific knowledge about diseases and their heritability. Lay people may instead use, for instance, their personal experience of diseases. Furthermore, both lay and professional perspectives are contextualized in different social and cultural contexts. Structure of research and healthcare systems as well as cultural ideals (Press, Fishman, & Koenig, 2000) are likely to shape perspectives on how genomic information should be managed in practice. This study used quantitative and qualitative methods to explore lay perspectives on risks of common diseases and secondary findings of genome sequencing. Quantitative research is needed to gain overall understanding of how risk perceptions and health behaviours are related among the population, whereas qualitative research is needed to gain more nuanced understanding of how people make sense of new risk information. The context of the study is a Nordic society that has a tax-funded public healthcare and a highly educated population (Official Statistics of Finland, 2017).

2 THEORETICAL BACKGROUND

This study combines perspectives of health behaviour theories on risk perception and illness representations. Receipt of genetic secondary findings is conceptualized as a specific situation where receiving information on personal disease risk and disease characteristics may shift risk perceptions as well as illness representations. Risk information is not learned in a vacuum but within varied social contexts and individual life situations. People are not passive recipients of risk information but actively interpret it through their previous knowledge and beliefs (Gerrard, Gibbons, & Reis-Bergan, 1998). For example, interpretations of negative risk information may be self-defensive (Wright, 2010), and also unexpected risk information – regardless of whether positive or negative – is more likely to be considered unreliable and rejected (Renner, 2004). This study assumes that people's previous beliefs about diseases and their personal risks are an important part of the context where new hereditary risk information is interpreted and acted upon.

2.1 RISK PERCEPTION IN HEALTH BEHAVIOUR THEORIES

Several health behaviour theories, for example the Health Belief Model (Becker, 1974) and the Health Action Process Approach (HAPA) (Schwarzer, 2008) include perceived risk of a health outcome as one of the key components that preceed preventive action. There is some variation in how perceived risk is defined. Most commonly perceived risk is seen to consist of perceptions of likelihood and severity of a health outcome. Sometimes a distinction is also made between likelihood and susceptibility or vulnerability. In that case, likelihood simply refers to probability of an outcome, whereas susceptibility refers to personal vulnerability for it, irrespective of how common or likely the outcome is in general (Brewer et al., 2007).

Risk communication is a common strategy to promote health behaviour. It has two aims: people are informed about their health risks to promote *accuracy* of risk perceptions and *motivation* to change health behaviour to reduce the risk (Weinstein & Nicolich, 1993). For example, people are told that obesity and lack of physical activity are risk factors for CVD and type 2 diabetes, to encourage changes in physical activity and dietary behaviour. In practice, however, this is far from straightforward. People are not passive recipients of risk information but actively process the information by combining it with their previous knowledge and beliefs (Renner, 2004; Walter, Emery, Braithwaite, & Marteau, 2004), and successful health

behaviour change usually requires more than just risk perception (French, Cameron, Benton, Deaton, & Harvie, 2017).

The relationship of risk indicators and perceived risk is assumed to be bi-directional (Weinstein & Nicolich, 1993): risk behaviour is supposed to increase risk perceptions, which are expected to motivate preventive health behaviour changes, after which one is expected to re-adjust their risk perception. Risk perceptions may also be conditioned (Brewer et al., 2007). For example, a person who currently is not physically active may plan to increase their physical activity and thus perceive lower disease risks than their current activity level would indicate. Or, a person who currently has normal weight might believe that they will gain weight as they get older, and thus this person would perceive higher disease risks than their current body weight would indicate. For reasons such as these, interpreting research results on the associations of risk perception and health behaviour requires care and particularly needs to consider differences between cross-sectional and longitudinal study designs (Weinstein & Nicolich, 1993). When assessing whether risk perception predicts protective behaviour in longitudinal settings, it is important to take into account for the baseline level of the protective behaviour (Gerrard et al., 1998).

In addition to actual risk factors, cognitive tendencies may contribute to risk perception. Most people are unrealistically optimistic about their future health (Weinstein & Klein, 1996). This optimistic bias is highlighted when people consider risks that they can control, such as their health behaviour (Klein & Helweg-Larsen, 2002). On the other hand, people who experience depressive symptoms might be more pessimistic (Alloy & Ahrens, 1987), which could increase their risk perceptions irrespective of their risk factors. The same bias could contribute to genetic fatalism, i.e. deterministic beliefs that there are no ways to prevent disease if the risk is inherited (Senior, Marteau, & Peters, 1999).

Several health behaviour theories, including the Health Belief Model (Becker, 1974) and the HAPA, suggest that risk perception encourages health behaviour change, together with other social cognitive factors. The HAPA proposes a two-phase model of health behaviour change (Schwarzer, 2008). Intention for a health behaviour is formed in the *motivational phase*, which includes perceived risk, health action self-efficacy, and outcome beliefs as determinants of intention. Perceived risk includes perception of severity and likelihood of a health outcome, for example a chronic disease like type 2 diabetes. Outcome beliefs refer to beliefs about efficiency of available preventive methods, such as physical activity or weight loss. In addition to physical outcomes, outcome beliefs may concern social outcomes, such as social approval, or self-evaluative outcomes, such as feelings of self-worth (Bandura, 2004). Health action self-efficacy refers to a person's confidence that they are able to perform this preventive behaviour. Hence, a person who perceives they are at risk for diabetes and believes that physical activity and weight loss will efficiently prevent the illness, and believes they will manage

physical activity and weight loss, is expected to have an intention to be physically active and loose weight. According to HAPA, intention is translated into action in the second, *volitional phase*, through action planning and coping planning. Intention is expected to lead to long term action if one believes they are capable of maintaining the health behaviour (maintenance self-efficacy) and re-adopting it after relapse (recovery self-efficacy).

Lay perceptions of disease risks and beliefs about preventive possibilities are closely linked to beliefs about how different diseases are like and how they evolve. The theoretical perspective of lay illness representations conceptualizes how people make sense of various diseases. The perspective of illness representations has been found useful for examining lay perspectives on predictive genetic testing (van Oostrom et al., 2007b).

2.2 ILLNESS REPRESENTATIONS

Health professionals have detailed information on different diseases, but research suggests that lay people make sense of different diseases through more general aspects that apply to all types of diseases. The Common Sense Model (CSM) of illness representations suggests that lay people make sense of diseases through five general dimensions (Hagger & Orbell, 2003; Leventhal et al., 1980). These dimensions are cause, consequences, illness identity, timeline, and cure/controllability.

The *cause* dimension includes knowlegde and beliefs about what causes the given disease. Multifactorial diseases have several causes – health behaviour, environmental exposures, and genetics. Even when professionals and lay people agree on the factors that contribute to certain illnesses, they may emphasize each factor differently (Damman & Timmermans, 2012). Causes may also include psychological explanations like personality or stress (Moss-Morris et al., 2002). The *consequences* dimension captures beliefs about how the illness affects one's quality of life and functional capacity. *Illness identity* refers to how the illness is labeled and what its symptoms are; whether it is seen as a coherent entity that makes sense (Moss-Morris et al., 2002). *Timeline* concerns individual's beliefs about the course of illness, e.g. whether it is chronic and how its symptoms progress. The *cure/controllability* dimension includes beliefs about whether and how the illness can be treated: whether and how it may be cured or how its symptoms may be alleviated (Hagger & Orbell, 2003).

These five dimensions are expected to be used for making sense of all types of diseases. The CSM has been used in research on various types of diseases, including cardiovascular diseases (French, Cooper, & Weinman, 2006), hereditary cancer (Kelly et al., 2005), neurological disorders such as dementia (Hamilton-West, Milne, Chenery, & Tilbrook, 2010), and psychiatric disorders such as depression (Fortune, Barrowclough, & Lobban, 2004). There is also some evidence that these dimensions interact with each other. For example, if

a disease is perceived to be caused by genetics, people tend to consider biological preventive methods more efficient compared to behaviour based methods (Senior & Marteau, 2007), and this may also depend on the type of disease (Wright et al., 2012). A strength of the CSM is that it acknowledges the role of people's previous experiences of diseases, and that individuals have an active role in making sense of potential health outcomes of their behaviour (Harvey & Lawson, 2009).

Illness representations are also likely to influence people's preferences for which types of secondary findings they wish to receive, and this needs to be taken into account in genetic counselling (Shiloh, 2006). Previous quantitative research also suggests that illness representations are likely to contribute to ways of cognitive and emotional coping with predictive genetic risk information (van Oostrom et al., 2007b): serious consequences and long duration of the illness and and an ambiguous illness identity seem to promote distress and various coping behaviours. Dimensions of illness representations have been shown to predict attending treatment (French et al., 2006). This suggests that changing illness representations may also change, for example, treatment seeking. When people receive new risk information such as genetic secondary findings, they may use their illness representations to make sense about what it means for their life. Receiving secondary findings may also shift illness representations when one receives more detailed information on the disease in question.

2.3 CONCEPTUAL FRAMEWORK OF THE STUDY

The conceptual framework of this study combines perspectives of health behaviour theories on risk perceptions and illness representations (Figure 1), which are described above. In this study, perceived risk of disease is understood as a multidimensional construct that combines 1) perceived likelihood and 2) perceived severity of the disease. Perceived likelihood means an individual's evaluation of the odds that they will develop the disease in question (low/high). Perceived severity is conceptualized to consist of a) severity of the illness in medical terms (e.g. mortality, severity of symptoms) and b) severity in terms of lived experience of the disease, which includes how the illness may affect personal life and social relations (e.g. quality of life, stigma). Perceived severity in medical terms and as lived experience are seen as overlapping. By making this distinction I want to emphasize that severity of illness has many different aspects for a lay person who not only looks at the illness from the perspective of how and how efficiently it could be treated (medical perspective) but also how the illness would integrate into one's life as a whole.

In this study, several factors are expected to contribute to perceived risk. Perceived likelihood of disease is expected to follow from disease risk indicators, such as family history of the disease, health behaviour,

physiological risk indicators such as body weight and biomarkers (e.g. blood sugar), and genetic risk indicators such as secondary findings. Perceptions of severity of the disease, on the other hand, are expected to follow from illness representations. I consider that family history – previous experience of the disease – has potential to contribute to individuals' representations of different illnesses. Family history is hence expected to directly contribute to perceived likelihood and indirectly to perceived severity through illness representations.

The conceptual framework expects health behaviour to contribute to perceived risk, and vice versa. Changes in health behaviour may also shift physiological risk indicators. People are expected to re-adjust their risk perceptions when their risk indicators change, and also to reduce their risks by preventive actions when they perceive risk of disease.

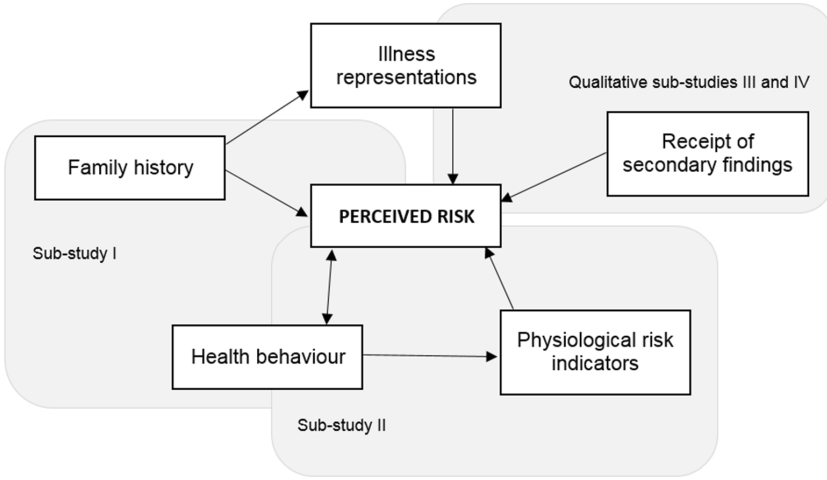

Figure 1 The conceptual framework of the study.

3 REVIEW OF EMPIRICAL LITERATURE

This literature review briefly describes empirical research concerning family history, disease risk perception, and health behaviour, as well as reactions to genomic secondary findings. Health psychological research has widely studied relationships of perceived risk of various health outcomes and different types of health behaviour (Sheeran, Harris, & Epton, 2014; Zhang, Schwarzer, Zhang, & Hagger, 2018). This review focuses on those theoretical models and health behaviours that are most relevant for the current study.

Risk perceptions tend not to be accurate evaluations calculated by objective risk factors (Adriaanse et al., 2008; Katapodi, Lee, Facione, & Dodd, 2004). In general, people tend to be optimistic about their future health, and they also tend to see their current health behaviour in favourable light (Rothman & Kiviniemi, 1999; Weinstein, 1984). Risk perception may be measured in absolute or comparative terms. Absolute measures may assess, for example, 10-year or lifetime risk perception on a five-point scale from very low to very high, or numerical scale from 0–100. Comparative risk perception measures risk relative to peers of the same sex and age; these tend to correlate moderately (Lipkus et al., 2000), and physiological risk indicators tend to associate more strongly with the absolute measures of perceived risk (Godino, van Sluijs, Sutton, & Griffin, 2014).

3.1 FAMILY HISTORY AND PERCEIVED RISK

Lay people tend to understand heritability as diseases and traits 'running in families', instead of a more detailed understanding of the structural and functional nature of genes (Condit, 2010a; Jallinoja & Aro, 1999). People acknowledge that diseases that run in the family may be caused by genetics and/or health behaviours which are shared by family members (Condit, 2010a). Those who are aware of the role of genetics are also more aware of the role of lifestyle in disease etilogy (Sanderson, Waller, Humphries, & Wardle, 2011). It has also been observed that perceived risks of different diseases tend to overlap (DiLorenzo et al., 2006), which could partly be explained by cognitive tendencies to view one's future health optimistically or pessimistically.

In previous studies, family history has had a strong association with perceived personal risk of CVD, type 2 diabetes and cancer (Acheson et al., 2010; DiLorenzo et al., 2006; Montgomery, Erblich, DiLorenzo, & Bovbjerg, 2003; Wang et al., 2012). Concerns have been expressed that knowledge of genetic risk could lead to fatalism and discourage any preventive health behaviour. However, empirical studies suggest that being aware of a familial or genetic risk for multifactorial diseases might have little impact on control

beliefs (Collins, Wright, & Marteau, 2011). Some studies even suggest it might increase feelings of control over the risk (McVay et al., 2015; Pijl et al., 2009) and incourage preventive action, including information seeking, screening attendance, and lifestyle changes (Hariri et al., 2006).

Research is still needed on whether family history is related to perceived risk independently of health behaviour. Also, previous studies have not explicitly compared the strength of this association across diseases in the general population. Furthermore, little is known about how family history contributes to perceived risks of psychiatric disorders, such as depression. There is some evidence that lay people are better aware of the social environmental risk factors of depression than the genetic component (Jorm et al., 1997), but it is unclear whether family history of depression contributes to perceived personal risk of depression. Family history and health behaviour could contribute to perceived risk differently across different types of diseases, which could have implications for risk education. Associations between family history and perceived risks of common diseases were examined in sub-study I of this thesis.

3.2 PERCEIVED RISK AND HEALTH BEHAVIOUR

Educating patients and the public about disease risks is a common health promotion strategy. However, risk perceptions are relatively resistant to new information and tend not to change easily (Wang et al., 2012), since people may psychologically reject or minimize personal relevance of risk information (Rothman & Kiviniemi, 1999; Vähäsarja et al., 2015). People may be self-defensive when faced with negative information (Gerrard et al., 1998; Wright, 2010), but they are also more likely to question reliability of risk information if it contrasts their expectations, regardless whether it is positive or negative (Renner, 2004). Some longitudinal studies provide evidence that people readjust their risk perceptions after they change their risk-related behaviour (Brewer, Weinstein, Cuite, & Herrington Jr, 2004; Renner, Schüz, & Sniehotta, 2008), but a recent review of 36 studies shows that simply providing personalized risk feedback usually does not lead to sustained health behavior change (French et al., 2017). Another systematic review of communicating coronary risk concluded that risk information may increase accuracy of risk perceptions and lead to preventive intentions, if it is repeated and combined with counselling, but simply providing risk estimates on a single occasion seems ineffective (Sheridan et al., 2010).

Health psychological research has widely examined the relationship of perceived risk and different types of health behaviour (Zhang et al., 2018), including getting vaccinated (Brewer et al., 2007), attending screenings (Katapodi et al., 2004), condom use (Foss, Hossain, Vickerman, & Watts, 2007), or physical activity and diet (Gholami, Knoll, & Schwarzer, 2014). Overall, previous evidence supports that perceived risk contributes to health

related behaviour, but its effect is likely to depend on the type of health behaviour. Risk perception seems to promote most clearly behaviours whose consequences are most clearly health related (Wright, 2010). For example, attending cancer screening or getting vaccinated is a more clearly defined health act, compared to physical activity or dietary behaviours that are integrated into people's daily social lives in complex ways.

There are also several studies that examined whether receiving biomarker based health feedback promotes health behaviour intentions. According to a review of randomized controlled trials (McClure, 2002), biomarker feedback may motivate health behavior change, but results from these studies are mixed. The review authors point out that these studies mostly used potentially biased retrospective self-report measures of behaviour change, and most of the studies did not measure risk perceptions, which could be the mechanism through which feedback motivates change. Feedback of physiological risk indicators of common diseases most likely needs to be combined with behavioural treatment (McClure, 2002), since lifestyle changes such as increasing and maintaining higher levels of physical activity or losing weight require sustained efforts. A recent review also concluded that communicating polygenic risks for multifactorial diseases tends not to result in health behaviour changes (Hollands et al., 2016).

Previous literature that examined physical activity using the HAPA model suggests that self-efficacy and outcome beliefs are more likely to promote intention to be physically active, whereas risk perception seems not to promote intention to be physically active (Gholami et al., 2014). Furthermore, intention to be physically active has an effect on actually being physically active (Gholami et al., 2014). Other studies, which looked at health behaviours more generally, concluded that risk perception had effects on health behaviour, but these effects were smaller than those of self-efficacy and outcome beliefs (Zhang et al., 2018). Self-efficacy has been linked with successful weight management in various intervention studies (Teixeira et al., 2015). A review on experimental studies, which looked at health behaviour in general, showed that risk appraisals did have small effects on intentions and health behaviour, and self-efficacy and outcome beliefs strengthened these effects (Sheeran et al., 2014).

Overall, previous literature suggests that risk perception has its place in behaviour change, but its role is likely to depend on the type of health behaviour in question, as well as other factors, such as self-efficacy and outcome beliefs. Hence, risk perception needs to be examined together with self-efficacy and outcome beliefs. As a result of health behaviour change, also physiological risk indicators such as body mass index (BMI) and blood glucose may change. However, no longitudinal studies have simultaneously assessed how perceived risk of chronic diseases, self-efficacy and outcome beliefs together relate to health behaviour and physiological risk indicators. This thesis addressed bi-directionality of perceived risk and risk indicators in sub-study II.

3.3 COMMUNICATING GENETIC RISKS: SECONDARY FINDINGS

Communicating traditional risk factors of chronic diseases has long traditions. Advances in genomics add a possibility to include genetic risks in risk communication. Genome sequencing makes it possible to calculate polygenic risk scores for multifactorial diseases, and to combine this information with traditional risk indicators, such as health behaviour, biomarkers, and family history. At the same time, however, genome sequencing raises the possibility to detect secondary findings that were not the primary target of the investigation: single variants that indicate high risks for heritable conditions.

Risks indicated by secondary findings differ from many other types of risk information in several ways. First, a single genetic variant may impose a high disease risk on its own, whereas polygenic risk scores usually impose less drastic changes to risk estimates based on traditional risk factors. Second, dominantly inherited high-risk variants concern also one's family members more clearly, since each first-degree family member has a 50% chance of having the same variant. Hence, individuals may feel strongly responsible for their family members in that situation (Vavolizza et al., 2015). Third, since secondary findings are 'secondary', they were not what was primarily expected from the analysis: the finding may be completely unexpected. In case of a clinical investigation, the primary target of a genomic analysis could be, for example, to diagnose a child who has a disability. A secondary finding could be, for example, a variant indicating high risk for cancer. This finding would have implications for the whole family, and it could be received in a situation where the family is already preoccupied by the child's current condition. Due to these complexities, a lot of discussion has been going on around how secondary findings should be handled in research settings and clinical practice.

Since there are dozens of possible secondary findings to be reported from genome sequencing, a lot of discussion has focused around what would be the best way to insure valid informed consent to receiving them (Appelbaum et al., 2014; Berg et al., 2011; Bunnik et al., 2012; Mackley et al., 2016). Traditionally, genetic testing for disease has been preceded with thorough counselling about the risk, the disease, and their implications. This practice aids individuals to make an informed decision on whether or not to have the test (Riley et al., 2012). Since it is not practical to provide extensive information on dozens of possible secondary findings, suggestions have been made about how secondary findings could be categorized, so that people could choose, which types of secondary findings they would like to receive (Appelbaum et al., 2014; Berg et al., 2011). These suggestions tend to conclude that secondary findings should be categorized based on severity of disease and efficiency of available preventive methods (Berg et al., 2011). It has also been suggested that

secondary findings linked to somatic and psychiatric diseases should be separated (Bunnik et al., 2012).

Overall, lay people seem to view positively the practice of reporting genetic secondary findings (Bollinger, Scott, Dvoskin, & Kaufman, 2012; Daack-Hirsch et al., 2013; Haukkala et al., 2013; Loud et al., 2016; Ormondroyd et al., 2007). Their preferences tend to be in line with professionals views in that majority prefers to know actionable secondary findings, however, their definitions of 'actionable' may differ from professional definicions of preventability and treatability (Mackley et al., 2016). To lay people, 'actionability' may also mean ability to plan one's life course or to help close ones prepare for the illness on time. Hence, for lay people, 'actionability' of secondary findings may be an ambiguous criterion when asking for consent to receive secondary findings (Jamal et al., 2017).

Research participants are usually positive towards receiving medically actionable secondary findings (Facio et al., 2013; Loud et al., 2016; Murphy et al., 2008). In fact, majority tend to respond that they wish to receive not only actionable but all possible results: those could be related to e.g. ancestry, pharmacogenetics, cardiovascular diseases, cancers, depression, Alzheimer's disease, Huntington's disease, or carrier status of recessive diseases (Wynn et al., 2017). In contrast to what professionals might expect, knowing one's risk for a non-actionable, progressive disease like Alzheimer's disease is not always perceived as most distressing, for example if one has reassuring previous experience of dealing with the illness, or if one believes that treatment methods will be available in the future (Jamal et al., 2017).

Several studies have examined research participants' reactions to genomic results (Hallowell et al., 2013; Haukkala et al., 2013; Lewis et al., 2016; McBride et al., 2016; Ormondroyd et al., 2007; Sanderson et al., 2017). In some studies that reported actionable secondary findings related to cancer or heart diseases, participants reacted positively and found the information useful (Haukkala et al., 2013; Lewis et al., 2016), but in other studies reactions to unexpected genetic risk information were more ambivalent (Hallowell et al., 2013; Ormondroyd et al., 2007). Qualitative research suggests that perspectives on secondary findings vary greatly according to individual life situations (McBride et al., 2016). Research is still needed on what types of support people need after receipt of secondary findings, and how these needs could be addressed in different contexts, as e.g. structure of health care system varies in different countries. This thesis addressed these issues in qualitative sub-studies III and IV.

4 STUDY AIMS

The general aim of this study was to examine lay perspectives on risks of common diseases and secondary findings of genome sequencing. Quantitative sub-studies I and II examined relationships between family history, perceived risk, physiological risk indicators and health behaviour among the general population. Qualitative studies III and IV focused on a specific situation of receiving genetic risk information. These studies explored lay perspectives on receiving different types of health related secondary findings from genome sequencing. Aims and research questions of each sub-study are detailed below.

Sub-study I: Is family history related to perceived risk of diabetes, CVD cancer, and depression? Are these associations similar across diseases, and independent of sociodemographics, BMI, health behaviour, and current depressive symptoms?

Sub-study II examined longitudinal associations of perceived risks and risk indicators over five years, among two samples with a different diabetes risk status. Does perceived risk of diabetes or CVD predict physical activity, BMI or blood glucose? Or rather, does physical activity, BMI or blood glucose predict perceived risk of diabetes or CVD? The study further examined how perceived risk, self-efficacy, and outcome beliefs together predicted changes in risk indicators.

Sub-study III explored Finnish adults' perspectives on the reporting of genetic secondary findings via letter. What are lay people's concerns and needs related to receiving genetic secondary findings that are linked to serious but actionable conditions?

Sub-study IV focused on meanings of different diseases in the context of secondary findings. How do lay people react to different types of hypothetical genomic secondary findings? In which ways does the type of disease matter when receiving genetic secondary findings?

This study used both quantitative (sub-studies I and II) and qualitative methods (sub-studies III and IV) to gain general understanding of risk perception in relation to risk indicators, and nuanced understanding of lay perspectives on hereditary risk information. There are several ways in which qualitative and quantitative methods may be combined (Johnson, Onwuegbuzie, & Turner, 2007), of which this study considers these approaches as complementary. Quantitative methods were used to gain an overall understanding of how lay people evaluate their risks for multifactorial diseases, whereas qualitative methods were used to gain detailed insight into how people make sense of new genetic risk information. Since the topics of quantitative and qualitative sub-studies were somewhat different, quantitative and qualitative data were not triangulated during the analysis process. However, these perspectives are seen as complementary when interpreting the study results.

5 QUANTITATIVE METHODS

Quantitative methods were used to gain an overall understanding of how family history, behavioural and physiological risk indicators, and depressive symptoms relate to perceived risks of common diseases among the Finnish adult population (sub-studies I and II). Main statistical methods were multivariate regression analyses and structural equation modelling.

5.1 PARTICIPANTS

The quantitative sub-studies I and II used national FINRISK health examination and survey data collected by the National Institute for Health and Welfare. FINRISK (The National Cardiovascular Risk Factor Survey) is a population study on chronic disease risk indicators that has been carried out every five years since 1972. The study uses independent, random and representative population samples from various areas of Finland. Sub-study I used a cross-sectional data of a nationally derived sample. Sub-study II used two sub-samples with a different diabetes risk status, who were followed-up during a five-year period. Research protocols were designed and conducted in accordance with the Declaration of Helsinki guidelines for research with human participants, and approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa. Each study participant gave a written informed consent.

5.1.1 FINRISK 2007

Participants of sub-study I were 25–74-year-old Finnish men and women who attended the National FINRISK 2007 study (Vartiainen et al., 2010). The study was conducted between January–March 2007. The study derived a random sample of 10 000 people from the population registry. The sample was stratified by gender, ten-year age-groups, and five geographical regions. Participation rate of the study was 63% (N=6258). People were invited to participate via letter, which invited the recipient to attend a health examination at a municipal health care centre. Attached to the letter was a questionnaire, which the recipient was asked to fill in at home and return when attending the health examination. The questionnaire included sociodemographics, medical history, health behaviour, life satisfaction, social trust, and family history and personal risk perceptions of common diseases: diabetes, CVD, cancer and depression.

In April–June 2007, all participants of FINRISK 2007 were invited to attend the Dietary, Lifestyle and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) sub-study (N=5024, response rate: 80 %)

(Konttinen, Silventoinen, Sarlio-Lähteenkorva, Männistö, & Haukkala, 2010). This study included a health examination and several questionnaires, including a scale for depressive symptoms (Radloff, 1977). Sub-study I used the data from DILGOM study for analyses that concerned depressive symptoms.

5.1.2 FINRISK BLOOD GLUCOSE STUDY 2002–2007

Sub-study II participants were from the FINRISK 2002 study, which examined cardiovascular risk factors (Laatikainen et al., 2003). FINRISK 2002 study procedure resembles that of FINRISK 2007, which was used in sub-study I. FINRISK 2002 picked a random sample of 13 500 people from the population registry – stratified by gender, ten-year age-groups, and six geographical regions. By mail, people were invited to fill in a survey and participate a health examination in January–March 2002. After the health examination, participants received a feedback letter, which reported several biomarkers, e.g. their cholesterol levels and blood pressure. The letter also described normal scores for each measure, and what the participant could do to achieve normal scores, if their personal values were not within the normal range. These advice contained recommendations for dietary changes, losing weight, increasing physical activity, or contacting their personal doctor.

FINRISK 2002 participants of age 45–74 years (N=3513) were invited to participate FINRISK Blood Glucose study later in the spring of the same year, in April–June 2002. This study contained a 2-hour glucose tolerance test and a diabetes risk factor questionnaire (Lindström & Tuomilehto, 2003). Participants (N=2558, participation rate 73%) received feedback of their fasting plasma glucose, 2-hour glucose, and insulin level via another feedback letter. The letter adviced the participant to have their glucose level re-measured, if their fasting glucose level exceeded 6.0 mmol/l, or if their 2-hour glucose exceeded 7.8 mmol/l, since these are considered elevated levels. The participant was adviced to contact a physician if their fasting glucose exceeded 7.0 mmol/l, or if their 2-hour glucose exceeded 11.1 mmol/l. These latter values are diagnostic criteria for diabetes, but individual diagnosis requires repeating the measurements (WHO, 1999), this information was not provided in the letter. In addition to these recommendations, the letter described that increasing exercise, decreasing fat intake, increasing fibre intake, or weight loss down to normal weight are means to reduce mildly elevated blood glucose.

Five years later in 2007, all FINRISK Blood Glucose Study participants who had a high risk for diabetes were invited to a follow-up. Diabetes risk was evaluated based on blood glucose measures, diabetes risk factor questionnaire (Lindström & Tuomilehto, 2003), or current or previous CVD. Participation rate was 80% (N=432). In addition, a random sample of those participants who were not classified as having high risk for diabetes were invited to the follow-up. Participation rate for this low/moderate risk sample

was 84% (N=477). The follow-up study 2007 included another survey and health examination with a new 2-hour glucose tolerance test. Sub-study II used these two sub-samples with a different diabetes risk status.

5.2 MEASURES

Perceived risks of diabetes (sub-studies I and II), CVD (I and II), cancer (I), and depression (I) were measured with single items: 'How do you perceive your own risk of developing [disease] in your lifetime?' 0=I have [disease], 1=very low, 2=low, 3=moderate, 4=high, 5=very high. A similar five-point scale has shown high correlation with a more continuous measure of perceived absolute risk during lifetime, and moderate correlation with perceived risk compared to other people of the same gender and age (Godino et al., 2014).

In sub-study I, participants who self-reported CVD (N=292), diabetes (N=191), severe depression (N=61), or previous or current cancer (N=184) were excluded from analyses concerning that disease. Similarly in sub-study II, those who self-reported diabetes/CVD were excluded from analyses where the relevant measure was used (diabetes at baseline: N=1 among high risk sample; at follow-up: N=2 among low/average risk sample, N=38 among high risk sample. CVD at baseline: N=20 among low/average diabetes risk sample, N=35 among high risk sample; at follow-up N=29 and N=36, respectively).

Family history (I) of diseases were assessed using sum variables that combined items concerning diagnosed diseases among first-degree family members. Family history of CVD consisted of whether a) father, b) mother, c) one or more brothers d) one or more sisters of the participant had had a myocardial infarction before the age of 60 (in case of mother 65). Family history of diabetes, cancer and depression consisted of whether a) father, b) mother, c) one or more brothers, d) one or more sisters had a diagnosis for that disease. Hence, available scale for each family history variable was 0–4.

Health action self-efficacy (II) was assessed with six items (reponse choices from 1=very uncertain to 4 completely certain): 'How certain are you that…

…you can take health perspective into account when planning your life and making decisions about it?

…you manage to follow your decisions on starting a new, healthier life?

…you manage to follow healthy lifestyle, even if people around you would not care about it?

…you can resist temptations when you know they harm your health?

…you manage to care about whether something is harmful for health or not, even if you are busy, tired, or under a lot of pressure?

…you can take health perspective into account, even if it would be inconvenient or you would have to give up other things that are important to you?

The questionnaire included three additional items that were excluded: one concerned smoking and another one adherence to health examinations, which

were not directly relevant for the study outcomes. One item was ambivalent in terms of content, whether it concerned self-efficacy or outcome beliefs. Self-efficacy was used as a latent variable in the analyses. Test of the combined measurement model of self-efficacy and outcome beliefs is presented in the results (section 7.2).

Outcome beliefs (II) were assessed with three items:
'How certain are you that serious illnesses such as heart diseases, cancer or diabetes can be prevented by healthy lifestyle?' (1=very uncertain to 4=completely certain).
'Heart diseases can be prevented by healthy lifestyle' (1=strongly disagree to 5=strongly agree).
'Changing diet at middle age is not worth it anymore' (1=strongly disagree to 5=strongly agree, reversed).

The questionnaire also included an item concerning whether it is worth it to change lifestyle if one is already ill, but this was excluded as it would not be relevant among a currently healthy population. Also outcome beliefs was used as a latent variable.

Physical activity (I and II) was measured slightly differently in sub-studies I and II. In sub-study I, the following item was used: 'How much do you exercise and strain yourself physically in your free time?' 1=reading, television or physically non-exhausting work at home (sedentary), 2=walking, cycling or similar at least 4 h/week excluding travel to work (moderately active), 3=vigorous exercise or work at least 3 h/week and 4=competitive training of strenuous sports several times a week (active, combined for group comparisons). This four-point measure correlates moderately with accelerometer counts among the working age population, and its criterion validity against morbidity and mortality is good (Fagt et al., 2011).

In sub-study II, a different single item was used: 'How many times a week, in your free time, do you exercise so that you experience at least mild exhaustion and sweating?' At follow-up, the question specified that each reported exercise time should take at least 20 minutes. Also response choices were added: 1=I cannot exercise due to illness or injury (excluded from analyses concerning physical activity, low/moderate risk sample N=13, high risk sample N=38), 2=less than once a week, 3=once a week … 7=five times a week or more. For the analyses, both measures were coded as 'physical activity': 0=less than once a week, 1=once a week, 2=twice a week, 3=three times a week, 4=four times a week, 5=five times a week or more.

Smoking (I) included three categories, 1=never smokers, 2=former smokers and 3=current smokers. Current smoking was defined as smoking regularly more than once a day for at least one year, including the preceding month.

Alcohol consumption (I) was measured as grams of pure alcohol per week during the past 12 months. This was calculated based on participants' responses to questions that asked about how frequently and how much they consumed different alcoholic beverages (Dufi'y & Alankoz, 1992). Skewness

(4.55) and kurtosis (28.07) of the distribution were reduced by using square root transformation before correlative and regression analyses were conducted.

Body mass index (BMI kg/m², I and II) was calculated based on weight and height, which were measured by trained research nurses.

2-hour plasma glucose (II) was measured in sub-study II health examinations at baseline and at follow-up. At baseline 2002 and at follow-up 2007, participants attended glucose tolerance tests, which were conducted according to WHO guidelines (11). After a 12-hour fast, each participant drank 300 ml solution with 75 g anhydrous glucose and 1.6 g citric acid. Blood sample was drawn after two hours for testing glucose level. (Borodulin, 2006) Compared to fasting glucose, 2-hour glucose predicts progress of diabetes more sensitively (Saaristo et al., 2010; Shaw et al., 1999), this is why 2-hour glucose was chosen as an outcome measure for the study.

Depressive symptoms (I) were assessed using the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). CES-D is a brief, structured self-report measure, which is not a diagnostic tool, but instead was developed for measuring depressive symptoms among the general population. The measure emphasizes the affective component of depression, i.e. depressed mood. The scale includes twenty statements that express feelings or behaviour during the past week, e.g. 'I felt that everything I did was an effort' and 'I was happy' (reversed). Response choices are 'Rarely or none of the time (less than 1 day)', 'Some or a little of the time (1–2 days)', Occasionally of moderate amount of the time (3–4 days)', and 'Most or all of the time (5–7 days)'. In the current study, number of days were not included in the response choices, but only the verbal descriptions.

Education years (I) were assessed using a single item: 'How many years have you attended school or studied full time altogether?'

5.3 STATISTICAL ANALYSES

The main statistical methods were multivariate regression analysis in sub-study I and structural equation modelling in sub-study II. These were conducted using SPSS Statistics version 24 and SPSS Amos Graphics version 24 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to explore distributions, means, and standard deviations of the study variables.

5.3.1 MULTIVARIATE REGRESSION ANALYSES

In sub-study I, bivariate correlations between study variables were examined using Pearson's correlation coefficients. We tested whether the correlation between family history and perceived risk was similar across diseases – diabetes, CVD, cancer, and depression. To test these, a calculation to test the

difference between two independent correlation coefficients was used (Preacher, 2002).

Sub-study I used multivariate regression analyses to examine whether family history (step 1), sociodemographics (gender, age and education, step 2), health behaviours (physical activity, smoking, alcohol consumption) and BMI (step 3), and depressive symptoms (step 4) explained perceived risk. These models were performed separately for each disease. Gender (0=men, 1=women) and smoking (0=never smokers/ex-smokers, 1=current smokers) were used as dichotomous variables in the correlative and regression analyses. All other variables were used as continuous variables.

To test whether sociodemographics, health behaviours, BMI, or depressive symptoms moderated the association between family history and perceived risk, separate models were used for each tested moderator. Each model contained main effects in step 1, and the interaction term in step 2. For education, also age was included in the first step, to take into account that the general education level has increased in Finland during the past decades. For smoking, current smokers and former smokers were compared against never smokers. For physical activity, moderately active and active participants were compaired against sedentary participants.

5.3.2 STRUCTURAL EQUATION MODELLING

In sub-study II, the main analytical approach was structural equation modelling, SEM (Lomax & Schumacker, 2004). This approach had several advantages in the current study: it allows multiple-group analyses, takes into account covariation of multiple predictors, and allows the use of latent variables, which reduces the effect of measurement error. All SEM models were adjusted for age and gender, and tested separately among the high diabetes risk sample and the low/moderate risk sample.

Longitudinal associations of perceived risk of diabetes/CVD and risk indicators (physical activity, BMI, 2-hour glucose) were examined using cross-lagged autoregressive models. Multigroup analyses were used to test whether the associations were similar among those with a high diabetes risk and among those with a low/moderate risk. Fit of cross-lagged models were not evaluated, as these were saturated models with zero degrees of freedom.

SEM was further used to test how perceived risk of diabetes, self-efficacy and outcome beliefs in 2002 predicted physical activity, BMI, or glucose level in 2007 (adjusted for baseline level of outcome variable). Similar models were performed to test how perceived risk of CVD, self-efficacy, and outcome beliefs in 2002 predicted physical activity and BMI in 2007. These models were evaluated using the following fit indexes: χ^2 statistic, Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), and Root Mean Square Error of Approximation (RMSEA) (Hu & Bentler, 1999). In all these models, self-efficacy and outcome beliefs were latent variables. The combined

measurement model of self-efficacy and outcome beliefs was tested before these SEM models were performed (see section 7.2).

6 QUALITATIVE METHODS

Qualitative methods were used to explore lay perspectives on secondary findings of genome sequencing. The qualitative approach was chosen to reveal nuanced experiences and meanings around the study topic. The qualitative sub-studies III and IV were based on a vignette study design (Barter & Renold, 1999), which included written reactions to hypothetical secondary findings, and focus group discussions (Barbour, 2008). The study is based on realist epistemology: the assumption is that written accounts and discussions are able to reveal something about 'experiences, meanings and the reality of participants' (Braun & Clarke, 2006). The study design was informed by the research tradition of Eskola's method of empathy-based stories, which has been used in Finnish social and educational research from the 1970s onwards (Eskola, 1998; Wallin, Helenius, Saaranen-Kauppinen, & Eskola, 2015). When using this method, the researcher creates a few variations of a story, after which the research participants are asked a question, answer to which provides one way to complete the story. The method resembles experimental desing in that answers to the different variations of the story may be compared against each other. A central strength of this method is its ability to encourage new perspectives on study topics, since it allows participants to think freely (Wallin et al., 2015).

The qualitative part of this study focused on four heritable diseases that all have autosomal dominant inheritance. In line with the method of empathy-based stories, the study participants were represented with a hypothetical situation of receiving a letter that revealed a secondary finding from clinical whole genome sequencing. Four versions of the vignette letter were formulated, each reporting risk for a different disease. The chosen diseases included two cardiovascular syndromes – familial hypercholesterolemia (FH) and long QT syndrome (LQTS) – and two cancer syndromes – Lynch syndrome (LS) and Li–Fraumeni syndrome (LFS). These diseases were included in the study since they are all among the list of secondary findings that the ACMG recommends to be reported in clinical settings (Kalia et al., 2016), but they vary in their severity and actionability. In addition, the research group had previous experience of reporting LQTS findings to biobank participants (Haukkala et al., 2013) and of contacting LS families via letter to invite them to have genetic testing (Aktan-Collan et al., 2007).

FH causes increased blood cholesterol, which needs to be medically treated. If untreated, FH leads to early coronary artery disease (Youngblom, Pariani, & Knowles, 1993). FH is relatively common among the population: in Finland its prevalence is estimated to be at least 0.17%, but it remains undertreated (Lahtinen, Havulinna, Jula, Salomaa, & Kontula, 2015). The other heart-related condition at the study focus, LQTS, predisposes to potentially fatal cardiac arrhythmia, usually before the age of 20.

Approximately half of non-treated mutation carriers have no symptoms, and the condition can be treated by beta blocker medication or pacemaker (Alders, Bikker, & Christiaans, 1993). The estimated prevalence of LQTS carriers in Finland is 0.01%–0.05% (Marjamaa et al., 2009).

The two cancer syndromes at the study focus differ in their actionability. LS predisposes to several cancers, particularly to early colorectal and endometrial cancers. However, colorectal cancer has efficient surveillance possibilities: mutation carriers are recommended to attend colonoscopy every 1–3 years (Kohlmann & Gruber, 1993; Seppälä, Pylvänäinen, Evans, et al., 2017), so that the neoplasia can be found and removed before they progress into cancer. Prevalence of LS carriers in Finland is around 0.0005–0.001% (Mecklin & Järvinen, 2007). The other cancer syndrome at the focus of this study, LFS, is a more rare syndrome, which predisposes to several types of cancers – e.g. soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumors, adrenocortical carcinoma, and leukemias – early in life, potentially already in childhood, and risk for multiple primary tumours is increased (Schneider, Zelley, Nichols, & Garber, 1993). Compared to LS, surveillance is less efficient, but mutation carriers are recommended comprehensive physical examinations annually, women are recommended annual breast magnetic resonance imaging and twice annual clinical breast examination, also prophylactic mastectomy and colonoscopies are options. Those who have the mutation predisposing to LFS have a 19% risk for cancer by the age of 30, and 90% risk by the age of 60. (Schneider et al., 1993)

The vignette letters that were used in the current study did not contain all the information described above. The vignette letters resembled real life letters that were used in earlier studies (Aktan-Collan et al., 2007; Haukkala et al., 2013). Before use, the vignettes were presented to and discussed with a pilot group of students. The research group considered that in real life, it would be unethical to reveal too detailed information on the diseases in a letter, since it could potentially cause excess distress. This is why the letters were quite brief and presented information at a general level: they did not describe risk percentages or worst-case outcomes. The four vignettes were parallel in their structure, but the level of detail for each disease varied slightly. The FH letter contained somewhat more detailed information on the condition, in order to convey that the condition is more severe than slightly elevated cholesterol level. Participants were given more information about the diseases during the focus group phase.

Similar to the quantitative sub-studies, the Declaration of Helsinki guidelines for research with human participants were used when designing and conducting the qualitative study. Each participant gave their written informed consent. Protocols of qualitative sub-studies III and IV were approved by the University of Helsinki Ethical Review Board in the Humanities and Social and Behavioural Sciences.

6.1 NEWSPAPER RECRUITMENT

Participants of the qualitative inquiry (sub-studies III and IV) were voluntary adults, recruited via Helsinki area Metro newspaper announcement on three days in May 2016, with the heading: 'How should hereditary risk information be delivered?' The announcement called for 18–64-year-old volunteers. Our research group was contacted by 32 people who were interested to participate and received a brief online survey. The survey was filled in by 29 participants, of whom 23 also attended one of four following focus group discussion. Participants who completed both study phases were compensated with two cinema tickets each. Sub-study III used focus group discussions to explore perspectives on secondary findings in general, whereas sub-study IV included immediate written reactions to hypothetical secondary findings, and those parts of the same focus group discussions that concerned meanings of different diseases in the context of secondary findings.

Out of the 32 people who were initially interested in participating the study, 29 participants completed a survey on sociodemographics and a writing task, and 23 attended one of the four focus group discussions. Only two of the participants were male; both participated also the focus group phase. The sample included a few younger adults, yet most were middle-aged (age range 20–64 years, mean 49). Out of all participants, 16 had own children, 12 had a university degree, and professions included e.g. entrepreneur, teacher, artist, salesperson, welder, accountant, archaeologist, nurse, and personal assistant. Family disease history was not systematically collected, but several participants brought up their family history of cancer, heart disease, or high cholesterol level during the focus group discussions. One of the participants was waiting to be genetically tested for a hereditary heart-related condition (other than LQTS or FH).

Out of those who completed the survey and writing task (N=29), six participants did not attend the focus group phase. Participants needed not provide reasons for not participating, but a few participants mentioned they were ill at the time of the focus group discussion, or could not find a baby sitter for the time. These participants were all female and roughly the same age as the rest of the participants (age range 30–61, mean 44). Sub-study III explored perspectives on receiving secondary findings at a general level, whereas sub-study IV explored meanings of different diseases in this context.

6.2 WRITTEN REACTIONS TO VIGNETTE LETTERS

The first phase of the procedure was a survey that was sent via e-mail. First, participants read a study info, and filled in a consent form online. Second, they filled in a brief sociodemographic survey. Third, participants were presented with a hypothetical scenario, which described a situation where they had

earlier had a medical examination for a non-specified reason. Participants were asked to imagine facing this situation in real life. The scenario described that their whole genome had been sequenced for a clinical investigation, and they had consented to receive also secondary findings in case there were any. Now, the letter said, there was a secondary finding predisposing the participant to one of the four diseases at study focus: LS, LFS, LQTS, or FH (randomly assigned). The letter briefly described the illness and its dominant inheritance, relevance to family members, possibilities for preventive treatment, and adviced the participant to contact health care. Fourth, the participants (N=29) wrote down what they would think and do if they faced this situation in real life.

6.3 FOCUS GROUP DISCUSSIONS

The second phase of the procedure was focus group discussions. Each participant (N=23) attended one of the four focus groups within seven days after completing the writing task. Each of the four sessions (duration: 94–125 min, mean 114) contained 4–7 participants. During each session, half of the participants had written their reaction on a cancer risk letter, and half on a cardiovascular risk letter. During the session, all participants could read both letters and comment on both of them freely.

I was the main facilitator of the focus group discussions, using a topic guide that covered first reactions to the letter, perceptions of disease and risk, searching for information, family, recommendations for implementation, and consent. Participants were encouraged to discuss the letter and the topic from various perspectives. Aktan-Collan co-facilitated the discussions, with the role of a medical expert and psychotherapist who could answer participants' questions on the diseases during the discussion. In addition, she introduced a brief slide show (14–32 min, 13 slides), which provided more information on the two diseases under discussion. This slide show was presented after approximately 45 min of discussion, in order to observe whether perspectives on the secondary findings would change after receiving more information on the diseases in question.

6.4 INDUCTIVE THEMATIC ANALYSIS

The written reactions and verbatim transcribed focus group discussions were analysed using inductive thematic analysis, with the help of the step-by-step guide provided by Braun and Clarke (Braun & Clarke, 2006). This flexible method aims to identify, analyse, and report patterns, i.e. themes within a data set. A 'theme' is a pattern within the data; a pattern that reveals something meaningful in relation to the research question. The method of thematic

analysis is compatible with both realist and constructionist epistemology, of which the current study is rooted in the former.

Sub-study III included the focus group discussions as data, whereas for sub-study IV we included the written reactions and those parts of the focus group discussions that concerned disease meanings. Sub-study III aimed to provide a rich description of the data set, whereas sub-study IV aimed to provide a more detailed account of disease meanings (Braun & Clarke, 2006). The analysis was inductive (data driven, 'bottom-up') in that it was not guided by theoretical premises; the data was not fitted to any pre-existing coding frames. The aim of the analysis was to reveal explicitly expressed opinions as well as to interpret implicitly expressed, underlying meanings (Braun and Clarke, 2006).

According to the step-by-step guide by Braun and Clarke, the phases of thematic analysis are 1) familiarizing with the data, 2) generating initial codes, 3) searching for themes, 4) reviewing themes, 5) defining and naming themes, and 6) producing the report. However, the process is not entirely linear but recursive, and different phases may overlap. I first read through the data entirely, to initially familiarize with it (step 1). Second, I systematically coded the data manually, writing codes for each bit of the data by hand on the transcript sheet margins (step 2). Third, I collected all the codes and created groups of codes that were related to each other, to form larger themes (step 3). Next, I discussed the content of the themes together with Aktan-Collan, who had also thoroughly familiarized with the data by reading it through several times. Aktan-Collan agreed with the content of the themes. I discussed the thematic map, presenting relationships between themes, together with Aktan-Collan and Hallowell. Specifics of the themes and the overall thematic structure was discussed and agreed among Aktan-Collan, Hallowell, and myself (steps 4 and 5). Furthermore, Aktan-Collan and Hallowell commented on several versions of the reports I wrote, so that best extracts to convey meanings of different themes could be decided upon (step 6). With the help of Hallowell, I translated data extracts from Finnish to English during report writing.

7 RESULTS

Results of the quantitative sub-studies showed that family history contributed to perceived risk across diseases independently of sociodemographics, health behaviour, BMI, or depressive symptoms. The longitudinal results, however, showed that perceived risk reflected risk indicators but did not predict preventive behaviour change. Qualitative results showed that despite being positive towards the practice of reporting secondary findings, people were concerned about availability of counselling and preventive treatment, and these concerns varied across different diseases.

7.1 FAMILY HISTORY AND PERCEIVED RISK

Sub-study I examined how family history, health behaviour and BMI, and depressive symptoms were related to perceived risk of common diseases. This study used cross-sectional data from the FINRISK 2007 study. Descriptive characteristics of the study sample are presented in Table 1. Means of perceived lifetime risks of different diseases ranged between 2=low and 3=moderate. Family history of cancer was the most common (36.7% reported at least one family member), followed by diabetes (28.4%), early myocardial infarction (25.3%), and depression (19.6%).

Pearson's correlation of family history and perceived risk was statistically significantly stronger for diabetes than any of the other diseases ($r=0.33$, $P<0.001$). Next strongest came CVD ($r=0.26$, $P<0.001$) and cancer ($r=0.23$, $P<0.001$). The association was statistically significantly weaker for depression than any of the other diseases ($r=0.19$, $P<0.001$). Differences in the strength of correlation were statistically tested (Preacher, 2002) and considered significant when $P<0.05$.

Correlations between perceived risks of different diseases were moderate (highest for CVD and diabetes, $r=0.43$, $P<0.001$) whereas correlations between family histories were weaker (highest for CVD and diabetes, $r=0.17$, $P<0.001$). Those whose BMI was higher perceived clearly higher risks of diabetes ($r=0.34$, $P<0.001$) and CVD ($r=0.25$, $P<0.001$), whereas health behaviour (physical activity, smoking, alcohol consumption) had weaker associations with perceived risks.

In multivariate regression analyses (Table 2), associations between family history and perceived risk (step 1) did not change after adding sociodemographics (step 2: gender, age, education years) or BMI and health behaviours (step 3) to the model. DILGOM sub-sample was used to add depressive symptoms (step 4), this did not change associations between family history and perceived risk of diabetes, CVD, and cancer. Depressive symptoms

did, however, have an effect on perceived risk of CVD (β=0.13, P<0.001), diabetes (β=0.16, P<0.001), and cancer (β=0.14, P<0.001).

Interaction analyses showed that, in general, health behaviours and BMI did not moderate the association of family history and perceived risk: only 3 out of 16 tested interactions were statistically significant (P<0.05). For sociodemographics, 6 out of 12 tested interactions were statistically significant (P<0.05). Associations of family history and perceived risk tended to be slightly stronger among younger and more educated participants, and – for perceived risk of depression – among women. Depressive symptoms did not moderate associations between family history and perceived risks of somatic diseases. Details of the interaction analyses are described in article 1.

Table 1. Descriptive characteristics of the FINRISK 2007 study sample (N=5744–6258).

	Mean (sd) or %	Min-Max
Women	53.1 %	
Age	50.8 (13.9)	25.0−74.0
Education years	12.8 (4.0)	0.0−50.0
Alcohol consymption (g/week)	76.4 (142.2)	0.0−1590.0
Body Mass Index (kg/m2)	27.1 (4.9)	16.0−63.3
Normal weight	36.0 %	
Overweight	40.4 %	
Obese	22.8 %	
Smoking		
Never smokers	53.9 %	
Former smokers	25.3 %	
Current smokers	20.3 %	
Physical activity		
Sedentary	20.3 %	
Moderately active	53.2 %	
Active	26.0 %	
Family history [1]		
Early myocardial infarction	25.3 %	
Diabetes	28.4 %	
Cancer	36.7 %	
Depression	19.6 %	
Perceived risk		
Cardiovascular disease	2.8 (0.9)	1−5
Diabetes	2.4 (0.9)	1−5
Cancer	2.7 (0.8)	1−5
Depression	2.0 (0.9)	1−5
Depressive symptoms [2]	10.2 (7.5)	0.0−51.0

[1] One or more affected first-degree relatives.

[2] Subsample N=4913.

Table 2. Results from multivariate regression analyses predicting perceived lifetime risk (FINRISK 2007).

		Cardiovascular disease (N=5445)				Diabetes (N=5529)				Cancer (N=5543)				Depression (N=5635)			
		B	SE B	β	Adj. R^2	B	SE B	β	Adj. R^2	B	SE B	β	Adj. R^2	B	SE B	β	Adj. R^2
Step 1					.07				.12				.05				.04
	Family history	.41	.02	.26***		.49	.02	.34***		.27	.02	.23***		.31	.02	.19***	
Step 3					.15				.22				.10				.06
	Family history	.39	.02	.25***		.45	.02	.32***		.31	.02	.27***		.30	.02	.19***	
	Gender [1]	.05	.02	.03*		.10	.02	.06***		.15	.02	.09***		.16	.03	.09***	
	Age	-.00	.00	-.00		-.01	.00	-.07***		-.00	.00	-.07***		-.00	.00	-.07***	
	Education	.01	.00	.04**		.01	.00	.02		.01	.00	.05**		.00	.00	.00	
	Smoking [2]	.20	.03	.09***		-.02	.03	-.01		.29	.03	.14***		.06	.03	.03	
	Alcohol	.01	.00	.04**		-.00	.00	-.00		.01	.00	.05***		.01	.00	.05***	
	BMI	.04	.00	.22***		.06	.00	.31***		.01	.00	.03*		.00	.00	.01	
	Physical activity	-.12	.02	-.10***		-.10	.02	-.08***		-.03	.02	-.02		-.13	.02	-.10***	

***P<0.001 (2-tailed).
**P<0.01 (2-tailed).
*P<0.05 (2-tailed).
[1] Men=0, women=1.
[2] No=0, yes=1.

7.2 LONGITUDINAL ASSOCIATIONS OF PERCEIVED RISK AND RISK INDICATORS

Sub-study II examined how perceived risk relates to behavioural and physiological risk indicators of diabetes and CVD over five years. Descriptive characteristics of sub-study II participants (FINRISK Blood Glucose Study 2002) are presented in Table 3. Means of perceived risks were higher among the high diabetes risk sample, but between 2=low and 3=moderate among both samples at both measurement points. However, at follow-up a third of the high risk sample were diagnosed with diabetes. Mean levels of baseline self-efficacy to make healthy choices were moderate (slightly below 3=quite certain). Mean level of outcome beliefs about possibility to prevent chronic illness through lifestyle were quite high among both samples.

In cross-lagged autoregressive models (for an example, see Figure 2), baseline perceived risk of diabetes did not predict physical activity, BMI, or 2-hour glucose after five years. In contrast, higher perceived diabetes risk at follow-up was predicted by higher glucose (high risk sample β=0.13, P<0.014), higher BMI (low/moderate risk sample β=0.15, P<0.001), and higher physical activity (low/moderate risk sample β=0.08, P=0.035) at baseline.

Similar cross-lagged models of perceived CVD risk showed that perceived risk of CVD did not predict physical activity or BMI over five years. Again, higher baseline BMI predicted higher perceived CVD risk (low/moderate risk sample β=0.10, P=0.006; high risk sample β=0.09, P=0.037). Physical activity did not predict perceived CVD risk. Results from all cross-lagged models were similar among both high risk and low/moderate risk samples ($\Delta\chi^2$-values 0.10–2.21, Δdf=1, P-values 0.137–0.752).

Table 3. Descriptive characteristics of the FINRISK Blood Glucose Study 2002 participants.

Baseline 2002	Low/moderate risk sample N=451–477	High diabetes risk sample N=390–432	Min–Max
Women %	57.7	56.9	
Age mean (sd)	55.9 (6.9)	59.3 (7.0)	45–74
Body mass index (kg/m2) mean (sd)	27.1 (4.2)	30.3 (4.7)	18.8–45.6
Body mass index ≥ 30, %	21.0	47.0	
Physical activity mean (sd)	2.5 (1.9)	2.4 (2.1)	0–14
2-hour glucose mean (sd)	5.8 (1.1)	9.2 (3.1)	0.7–29.5
Perceived diabetes risk mean (sd)	2.4 (0.9)	2.8 (0.9)	1–5
Perceived cardiovascular disease risk mean (sd)	2.9 (0.9)	3.1 (0.9)	1–5
Self-efficacy mean (sd) [1]	2.8 (0.5)	2.7 (0.6)	1–4
Outcome beliefs mean (sd) [2]	11.3 (1.7)	11.2 (1.8)	5–14
Follow-up 2007	**N=437–477**	**N=416–432**	
Women %	57.7	56.9	
Body mass index mean (sd)	27.0 (4.5)	30.2 (5.0)	17.7–48.3
Body mass index ≥ 30, %	21.9	47.1	
Physical activity mean (sd)	2.6 (1.5)	2.4 (1.6)	0–5
2-hour glucose mean (sd)	6.3 (1.9)	8.7 (3.0)	2.4–25.8
Perceived diabetes risk mean (sd)	2.4 (0.9)	3.0 (0.9)	1–5
Perceived cardiovascular disease risk mean (sd)	2.8 (0.8)	3.0 (0.9)	1–5
Glucose lowering medication %	0.6	11.1	
Onset of diabetes %	6.4	34.2	

[1] Available scale 1–4.
[2] Available scale 3–14.

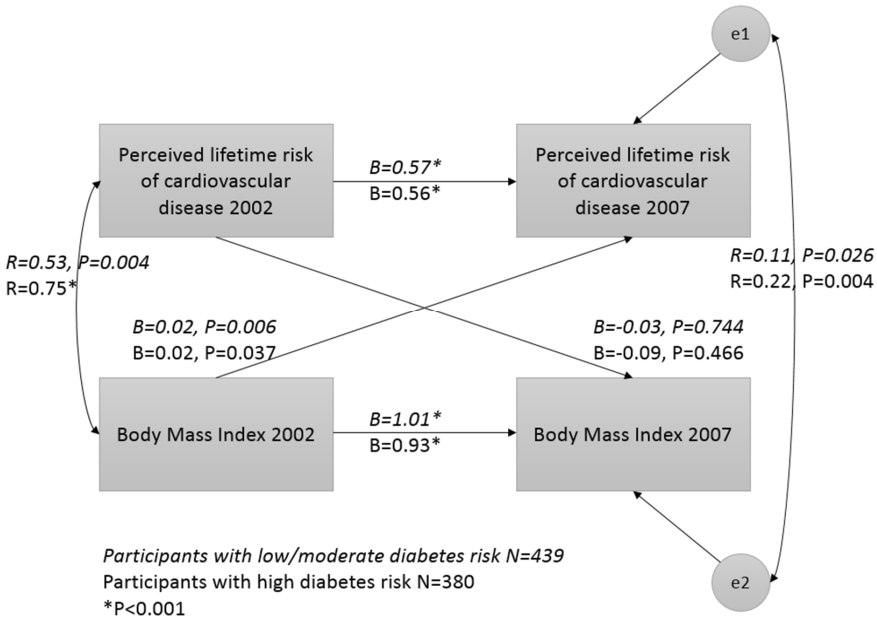

Figure 2 Unstandardized age- and gender-adjusted results from a cross-lagged autoregressive model (FINRISK Blood Glucose Study 2002).

The combined measurement model of self-efficacy (six items) and outcome beliefs (three items) showed reasonable fit (Hu & Bentler, 1999) with the data in the low/moderate risk sample (χ^2=153.99, df=26, P<0.001; CFI=0.910; TLI=0.845; RMSEA=0.102) and in the high risk sample (χ^2=113.51, df=26, P<0.001; CFI=0.935; TLI=0.887; RMSEA=0.088). Standardized factor loadings were highly similar among the low/average risk sample and the high risk sample (0.55–0.80 for self-efficacy, 0.33–0.69 for outcome beliefs, all P-values<0.001). Latent factors self-efficacy and outcome beliefs had a moderate, positive correlation in the low/moderate (r=0.28, P=0.001) and in the high risk (r=0.41, P<0.001) sample.

Further SEM models included perceived risk of diabetes/CVD, self-efficacy, and outcome beliefs (2002) as predictors of physical activity, BMI, and 2-hour glucose (2007). All models were adjusted for gender, age, and baseline level of outcome variable. Those who had a higher self-efficacy at baseline increased physical activity at follow-up (standardized β-values between 0.11–0.18, P-values 0.007–0.034). However, self-efficacy did not predict BMI or 2-hour glucose. Perceived risks of diabetes and CVD did not predict physical activity, BMI, or 2-hour glucose; nor did outcome beliefs.

In sum, the quantitative sub-studies showed that family history was related to perceived risk across different diseases, but perceived risk did not predict health promoting changes in behavioural or physiological risk indicators over

five years. Next sections describe results of the qualitative studies, which explored perspectives on receiving new risk information: secondary findings from genome sequencing.

7.3 NEEDS AND CONCERNS AROUND SECONDARY FINDINGS

Since the study scenario of the qualitative inquiry described a situation in which participants had already given their consent to receiving secondary findings, the focus group discussion mostly focused on the aftermath of receiving secondary findings, instead of consent procedures. Overall, participants thought reporting secondary findings for actionable diseases was acceptable and useful. Mixed feelings were also expressed, particularly towards the end of discussions. Mixed feelings seemed to arise when participants had had time to thoroughly elaborate complexities of the matter: magnitudes of risks, efficiency of treatment, consequences to social relations and individual identities.

In the midst of the discussions, participants were presented with a brief slide show that contained more information about the two diseases under discussion. Course of discussion did not remarkably change after receiving more information, but participants pointed out that the letters could contain some more information on the disease prevention, to avoid misunderstandings, distress, and avoidant reactions.

Five major themes were identified: *immediate shock*, *dealing with worry and heightened risk*, *fear of being left alone to deal with secondary findings*, *disclosing to family* and *support needs*.

Immediate shock

First reaction to the vignette letter was negotiating how shocking this information was. Some described the letter as a 'surprise' or 'bomb', whereas a minority stated the opposite: they 'did not take it very seriously' (D1=first speaker of focus group D). Some also pointed out that secondary findings could be a useful 'wakeup call', and remind one to 'live one's life to the fullest' (A6). Participants also emphasized that individuals have different tendencies to worry; young people, females and those with an anxious personality were considered more likely to get upset upon receiving secondary findings. It was evident that it was not socially acceptable to belong to this vague group of people who would get too upset and 'stick their head in the sand' (D3). Parallel to negotiations about how shocking the secondary findings were, the acceptable level of worry was negotiated. Participants wanted to appear sensible and capable of coping:

> D2: *but there are people who don't need but the zero point zero something per cent risk and still the anxiety, the fear hits them and they collapse, you know that kind of people*

D3: *on my part I certainly would think about the odds*
D2: *but that indicates courage. Then there are those who start to be fearful straight away before there is really anything at all*
D3: *yeah, but I just wanted to make clear, that I would not like push it away, like because of fear, but instead like through reason*

Hence, in addition to dealing with the shock of receiving secondary findings, participants needed to deal with an implicit social pressure to cope with it.

Dealing with worry and heightened risk

Participants recognized that after receiving secondary findings, dealing with the information would continue after the immediate shock. They expressed concerns that knowledge of risk could threaten quality of life and holistic well-being, or even evoke a self-fulfilling prophecy and trigger the illness to occur through 'stress', 'placebo effect', or 'energy':

> A6: *if we learn about a possibility to develop some illness, and then we give it both our own energy and our relatives' worry energy, and start to like dwell on it (--) so are you like actively activating the gene*

Too vigorous attempts to control one's health were disapproved, similarly as too emotional first reactions (described above):

> A7: *everything has to be so controlled (--) and then you just hysterically follow [guidelines of authorities] (--) like common sense is all lost [these days]*

Altogether, receiving secondary findings was seen as to require immediate as well as long term coping with distress. This potential distress was amplified as participants were concerned whether they would be left on their own to deal with it.

Fear of being left alone to deal with secondary findings

Focus group participants emphasized that immediately after receiving secondary findings, support via phone or personal contact should be easily available. They also brought up that individual life situations would likely contribute to how much support would be needed. Young people were, again, seen as more vulnerable, as risk information could affect their life choises or isolate them from their peers:

> D2: *how on earth would a [15-year-old] person who wants to be like everyone else bear having this kind of very rare thing [risk for LFS], so it would be even worse, at a certain age*

In contrast, at an older age, threat of illness would be more commonplace and not so threatening to social relations.

Concerns of being left alone to deal with secondary findings were contextualized within the Finnish healthcare system and society in general. Participants explicitly pointed out that reporting secondary findings would be

more acceptable in equal, just societies with a well-functioning healthcare system:

> A7: *we have exceedingly skilled clinical professionals, and our doctors and research and everything are really top-notch, like the care one receives in Finland is so good so I definitely wouldn't be worried one bit*

It was argued that in a society where not everyone has access to relevant treatment and care, reporting secondary findings could benefit the well-off and harm the disadvantaged:

> B1: *if the society is like just and equal, then people might be more ready to receive the [secondary finding] information, because they would feel they are safe (pause) but if it's a very unequal society, and everything is like going in a bad way (pause) then it could be, it's hard to say, then everyone acts more (pause) from their own stances. Some flush their lives down the toilet and some [other interviewee: pull themselves together] yeah, pull themselves together*

Worry about being left alone to deal with secondary findings was also linked to concerns about how this information should be communicated to family members.

Disclosing to family

Disclosing secondary findings was seen as a difficult task even for professionals. Hence, participants were concerned how they would be able to disclose this information to their family, and whether there would be support available for this. Participants expressed concerns about their family members' health but also how disclosing such information might affect family relations. Participants felt responsible to disclose but also to protect their relatives, particularly children, from worry.

> C4: *you really have no answers to questions that could arise in that situation, so it would be quite a scary situation, I mean informing others, how to then do it so that the other one doesn't panic altogether*

Consequently, when thinking of disclosing secondary findings to others, one no longer was in the position of needing support, but in the position of the one who has the responsibility to provide support.

Support needs: information, access to care, empathetic communication

Three types of intertwined support needs to tackle concerns described above were identified. Participants emphasized that after receiving secondary findings, access to reliable and reassuring information about the disease risk and its implication would be crucial for coping, since 'these days you can find all kinds of [scary and unreliable] things on the internet' (D1). Information

about preventive and treatment methods would help to gain control over the situation.

> A5: *at first you panic, but the more you get to know about the matter, the easier it gets. And then if you know, like (pause) how it's treated. To me that's always the most important, that I know how to go forward, and how I can survive this (pause) so, I think this letter is very good. And the fact that you can contact, probably I would contact them (pause) so (pause) I would like to discuss it further with an expert*

Similarly to participants A5 above, many participants pointed out that a personal contact with an expert would be important. However, participants also strongly expressed concerns that not all professionals might be able to provide this information in the right way. The right way would be empathetic communication.

> D4: *it has an enormous impact, what kind of (pause) conversation you can create then, and plan for further care, that gets you through everything*

Need for information was intertwined with an emotional need to be taken care of and treated in a respectful manner. This would promote feelings of safety and being valued.

7.4 TYPE OF DISEASE MATTERS WHEN RECEIVING SECONDARY FINDINGS

Sub-study IV focused on meanings of different diseases in the context of secondary findings. In addition to focus group data, the study included immediate written reactions to vignette letters. First reactions varied from neutral or grateful to terrified, angry, or regret over consenting to receive secondary findings. The major themes were *familiarity*, *severity in terms of lived experience*, *cancer vs. heart disease*, *somatic vs. psychiatric disease*, *access to treatment*, *stigma*, and *responsibility*. To protect anonymity of written reactions, they are referred to by participant numbers (P1–P29), and focus group comments similarly as above (A1=first speaker of focus group A).

Interplay of familiarity and severity of disease

Individual earlier experiences and familiarity of the disease strongly shaped first reactions. The power of previous experiences was clearly demonstrated by the written reaction to the LS letter of a participant whose father had died from colorectal cancer: 'I'm terrified (--) I will call the hospital immediately for further instructions (--) I don't want the same destiny (--) I would die slowly too' (P4).

Comparing reactions to the four diseases at focus is extremely tentative, since individual reactions varied greatly. However, reactions to FH tended to be brief and neutral: 'I would act according to the recommendations in the

letter' (P20). The letter for LQTS evoked questions about what the disease is like: 'I would be frightened at first and wonder what this information really means for my own and my possible child's life' (P23). Shock upon the LS letter was alleviated by the preventive method that were mentioned: 'Sure the information would be overwhelming for a moment (--) I would find out about the treatment/prevention possibilities as much as I can and start trying those' (P1). Written reactions to the LFS letter were lengthier and more emotional. 'Maybe I shouldn't have signed the consent for contact. First feeling is despair, in particular if I have children at this point, I mean worry for children' (P10).

Cancer vs. heart disease

Earlier experiences and knowledge about diseases influenced not only written first reactions but also further elaborations during the focus group discussions. Overall, cancer related letters were considered more threatening compared to cardiovascular related letters:

> B2: *my heart would've probably been racing more if I had read this cancer thing. In my opinion everybody has cholesterol, and it's not fatal straight away, so I think these [letters] are on a completely different level*

> D1: *I somehow, indeed, well I didn't take very seriously that disease [LQTS] (laughs) I just read it and like 'so what'. So if I had received this cancer letter [LFS] I might have responded differently. Cancer as a word is worse straight away, it takes you aback in itself.*

However, participants commented that cancer related findings would still be less distressing than genetic risk information for psychiatric disorders.

Somatic vs. psychiatric disease

Unexpectedly, three out of four focus groups pointed out that receiving genetic risk information for psychiatric (e.g. schizophrenia, bipolar disorder) or incurable neurological disorders (Alzheimer's disease), alcoholism, or intellectual disability of children would be more distressing compared to the somatic diseases described in the vignette letters. They outlined several reasons for this. Overall, psychiatric and somatic diseases were differentiated in four ways. Psychiatric disorders were perceived more burdensome in their 1) severity in terms of lived experience of disease, 2) treatability and access to treatment, 3) level of stigma, and 4) individual's responsibility for managing the risk.

Participants said that living with psychiatric disorders and Alzheimer's disease is very hard for individuals and families. This is why the idea of receiving such risk information was distressing.

> A4: *I would rather have [my children] with a physical illness [*A2*: So would I], because life is pretty horrible with those fears and delusions*

Access to treatment

Psychiatric risks were also seen as hard to live with because participants perceived it is hard to get efficient early psychiatric treatment.

> A7: *if I have a (pause) some kind of physical illness, they won't tell me that 'Well let's wait until you rot, then we will take you in for treatment' but they will start to examine [*A2*: Yeah] based on first symptoms to find out what it could be and as soon as possible start medication and treatment so that it will not get worse [*A2*: It's about attitudes] but for psychiatric illnesses it's completely the other way around*

With poor access to treatment, individuals were implicitly regarded as more responsible for managing psychiatric risks on their own. This contributed to implicitly blaming individuals for their psychiatric problems and increasing their stigma.

Stigma and responsibility

Psychiatric disorders were seen as more stigmatized than somatic diseases: 'stigma is thrown upon the whole family [when psychiatric disorder occurs]' (A2).

In a more implicit manner, it was evident that perceptions of responsibilities of individuals and health care system influenced how participants made sense of potentially receiving genetic risk information for psychiatric disorders. Knowledge of risk could be seen as a burden or a relief. Treatment of somatic diseases was seen as the responsibility of the healthcare system, more so that treatment of psychiatric disorders. This was partly because early psychiatric treatment was seen as scarcely available as described above: individuals need to take responsibility if the health care does not do it. In addition, the nature of psychiatric diseases played a role in these perceptions. Since psychiatric disorders or alcoholism tend to show observable early symptoms, individuals were seen as responsible to monitor and cope with these symptoms. Knowledge of genetic risk could increase control over the risk but also pose the individual additional burdensome responsibility.

> A7: *I think also with mental health problems [similar to alcoholism] (--) I can pretty well analyze my own behavior after all (--) Say for example if you have depression in your family. (--) But for this type of physical illnesses, you can't, if they show no symptoms, you can't do anything [to monitor it]*

> B1: *when you know there is a hereditary risk for depression in your family (--) then you can start to, build your life or your lifestyle, take it into account, like for example 'I have to avoid extreme stress, because stress predisposes to depression' (--) or hereditary susceptibility to alcoholism, also then, when the person knows it, they can influence, so that it is perhaps best to stay away from using alcohol completely*

In contrast, individuals were not allocated a same level of responsibility in preventing somatic diseases even when their onset could be influenced by healthy lifestyle:

> B3: *suddenly life turns around, there comes an uninvited guest [=somatic disease] (pause) [--] we can't that well, we can't like earn a good life ourselves cause, cause verifiably people die of for example some horrible disease, even if they look so healthy and have lived so healthily, cause nothing is hundred percent certain*

In sum, level of stigma, access to treatment and nature of the disease itself shaped how burdensome receiving genetic risk information would be.

8 DISCUSSION

The quantitative part of this study found that family history contributed to perceived risks of common diseases independently of sociodemographics, BMI, health behaviour, or depressive symptoms (sub-study I). Family history contributed to perceived risk more strongly for somatic diseases – diabetes, CVD, and cancer – compared to depression. Over a five-year follow-up (sub-study II), however, perceived risk of diabetes or CVD at baseline did not predict health-promoting changes in physical activity, BMI, or blood glucose level. This was observed similarly among two samples with a different diabetes risk status who received individual biomarker risk feedback after study baseline. On the contrary, baseline risk indicators predicted slightly higher perceived disease risks after five years. Self-efficacy predicted slightly increased physical activity over five years, but outcome beliefs did not predict physical activity, BMI, or blood glucose.

The qualitative part of this study revealed that even when people think returning secondary findings from genome sequencing is useful and acceptable, they may worry about whether counseling or relevant surveillance and preventive care are available for individuals and families (sub-study III). The results underline the importance of taking into account the societal context, including different health care systems, when evaluating acceptability of secondary findings reporting practices. The results also suggest that genetic risk information may be more threatening when it concerns cancer compared to heart-related conditions, but genetic risk information for psychiatric disorders could provoke even more distress (sub-study IV). Lay perceptions of disease severity and treatability may be heuristic and possibly not always in line with expert knowledge on specific diseases and their treatment possibilities.

In this section I will first focus on elaborating results on risk perception and health behaviour, and then continue to discuss the results on secondary findings. In the end, I will reflect on the methodology, and present my concluding remarks.

8.1 RISK PERCEPTION AND HEALTH BEHAVIOUR

Perceived risk of disease is expected to reflect actual risk factors, but also general cognitive tendencies. Indeed, perceived risks of different diseases were related to each other (sub-study I), as in previous research (DiLorenzo et al., 2006). In line with literature on unrealistic optimism (Weinstein & Klein, 1996), this study found that people tend to underestimate their risk: on average, those at high diabetes risk perceived their lifetime risk as moderate, but after five years a third of them already had diabetes (sub-study II). On the

other hand, sub-study I found that those who have depressive symptoms may be less optimistically biased since their risk perceptions tended to be higher. However, this pessimism seemed not to translate into genetic fatalism: one might expect that family history would contribute to perceived risk more strongly among those with depressive symptoms, but this was not supported by the data (sub-study I).

It is noteworthy that tendency to perceive risks was also discussed by the focus group participants of the qualitative inquiry. While individual responsibility for taking care of one's health was emphasized, tendency to worry in general was depicted as an undesirable personality characteristic. Optimistic risk perceptions could also partly reflect social norms according to which tendency to perceive risks is not a desirable characteristic. Some focus group participants explicitly linked tendency to worry with females, and this can be seen as stereotypical but also 'accurate', since women and disadvantaged ethnic minorities do tend to perceive higher risks in various life domains, compared to white males (Kahan, Braman, Gastil, Slovic, & Mertz, 2007). These observations show that risk perception is not simply rational calculation, but interacts with one's personal life in nuanced ways.

In the cross-sectional setting of sub-study I, family history was related to perceived risk across different multifactorial diseases: diabetes, CVD, cancer, and depression. This is in line with previous studies on risk perceptions of somatic diseases (DiLorenzo et al., 2006), and an earlier Finnish survey (Jallinoja & Aro, 1999), where diabetes and CVD were most frequently mentioned when participants were asked to name diseases that are hereditary. The population based data of this study showed that the relationship of family history and perceived risk was robust and did not change after accounting for sociodemographics and several health behaviours, BMI, and depressive symptoms, which could reflect a more pessimistic cognitive tendency. Furthermore, the large data made it possible to test interactive effects of family history and other factors in relation to perceived risk. Health behaviour and family history showed no systematic interactive effects on perceived risks. These findings support previous research, which suggests that lay people consider genetic and behavioural risk factors as adding to each other (Condit & Shen, 2011), meaning that people tend not to focus on the interactive nature of genes and health behaviour. Among younger and more educated people, however, family history tended to contribute to perceived risks slightly more strongly than among older and less educated people. Younger and more educated people are likely to be more aware of heritability of common diseases, since they have more knowledge about genetics (Haukkala et al., 2018; Jallinoja & Aro, 1999).

A new contribution of this study was that the association of family history and perceived risk was also observed for a psychiatric disorder, depression, at the population level. The association was weaker compared to somatic diseases. This could be related to measurement: perceived risk concerned only severe depression, and family history concerned only diagnosed depression.

People could often be unaware whether their family member had been diagnosed, even if the family member would show observable depressive symptoms. However, environmental risk factors for depression may be better known among the public, compared to hereditary risk for depression (Jorm et al., 1997). The qualitative results of the current study also suggest that possibility to monitor early psychiatric symptoms shapes how individuals evaluate their risks, which could result in less emphasis on their family history, compared to somatic diseases. More research is needed on how perceptions of causes of psychiatric disorders contribute to how individuals manage these risks.

The qualitative results of sub-study IV revealed that genetic risk information on psychiatric disorders could be more distressing compared to risks of common somatic diseases. This was an unexpected finding, as the vignettes and interview guide did not concern psychiatric risks. Reasons behind distress over psychiatric risks seemed to include potential stigma but also perceptions that early access to treatment is poorer for psychiatric compared to somatic diseases. What seemed to follow partly from poor access to treatment and partly from possibility to monitor early psychiatric symptoms was that individuals were seen to be left with more responsibility for managing psychiatric risks, whereas the public health care was seen to take more responsibility for somatic risks. Also previous literature has raised concerns that psychiatric genetic risks could potentially be more stigmatizing (Bunnik et al., 2012; Kostick et al., 2018), but the current study highlights that this may not only relate to the nature of illness itself but also to how treatment of different disorders is organized in different healthcare contexts.

This study also looked at bi-directionality of perceived risk and risk indicators in a longitudinal setting. The study results provided some support for accuracy hypothesis but not the behavioural motivation hypothesis of risk perception (Weinstein & Nicolich, 1993). People at high diabetes risk underestimated their risk, but nevertheless risk perceptions reflected behavioural and physiological risk indicators. During a five-year follow-up, however, perceived risk did nor predict health promoting changes in physical activity, body weight, or blood glucose. It should be noted that in the longitudinal setting of sub-study II, perceived risks of diseases were measured before and not right after participants received health examination based biomarker feedback. Biomarker feedback may have temporarily changed risk perceptions and behavioural intentions (McClure, 2002), but these could not be assessed in this study. Health examination based feedback is part of the FINRISK study protocol, but participants have only been asked to fill in questionnaires before health examination. If the biomarker feedback encouraged intentions to make lifestyle changes, it is possible that these were not accomplished in the longer term. These results stress that to accomplish sustained changes in weekly physical activity or weight, risk perception or biomarker feedback alone is likely to be inefficient. To encourage preventive intention, risk information should ideally be combined with counselling and

repeated measurements of risk indicators (Sheridan et al., 2010). Behaviour change techniques such as promoting goal setting and monitoring one's behaviour seem to make successful changes in physical activity and healthy eating (Michie, Abraham, Whittington, McAteer, & Gupta, 2009). The qualitative results of this study support the perspective of counselling, since focus group participants wished that when secondary findings indicating risk for disease are communicated, this should be combined with counselling and practical advice on how to reduce risk. Similar wishes for practical plans have been observed also in other qualitative studies on receipt of secondary findings (Daack-Hirsch et al., 2013).

In addition to risk perception, other social cognitive determinants need to be considered when aiming to prevent chronic diseases, as suggested by e.g. the HAPA model (Schwarzer, 2008). Similar to numerous previous studies (Gholami et al., 2014; Teixeira et al., 2015; Zhang et al., 2018), the current study showed that self-efficacy matters in health behaviour change. Self-efficacy predicted increased physical activity over five years (sub-study II). In contrast to previous research, however, outcome beliefs did not predict health promoting changes, but this may be explained by weakness of the used measure: only three items were included in the outcome beliefs latent factor, and factor loadings were only moderate. Overall, the current study results support previous studies' conclusions that risk perception alone is unlikely to lead to sustained health behaviour changes. This was observed similarly among those with a high diabetes risk and those with a low or moderate risk. Interventions need to target risk perceptions together with other social cognitive factors (Harvey & Lawson, 2009; Rimal, 2001; Sheeran et al., 2014). Finally, we need to keep in mind that risk perception is expected to predict *protective* behaviour. Risk perception seems to have the strongest effect on behaviours whose consequences mostly concern health (Wright, 2010). Physical activity and eating carry a complex set of meanings in people's lives; these behaviours are a lot more than means to prevent disease. This is likely to weaken the effect of perceived risks on such complex behaviours.

Perceptions of risks and different diseases serve as a context for receipt of new risk information. As an example of this, the qualitative inquiry of this study focused on the situation of receiving secondary findings from genome sequencing.

8.2 LAY PERSPECTIVES ON GENETIC RISKS

The theoretical perspective of illness representations (Hagger & Orbell, 2003; Leventhal et al., 1980) was identified as a useful perspective for making sense of how individuals approach new genetic risk information. The qualitative results of this study provided insight into detailed ways in which familiarity of disease plays a role when interpreting genetic risk information (sub-study IV).

Family history of disease not only provides information on personal risk but also most likely contributes to illness representations. Having had an illness in the family may provide tangible first-hand experience of the lived experience, the *consequences* of a disease, as proposed by the Common Sense Model of illness representations (Leventhal et al., 1980). In case one has no experience of the illness whose risk is communicated, one uses their experience and knowledge of illnesses that are somehow similar: focus group participants used their overall understandings of cancer when making sense of unfamiliar heritable cancer syndromes. Illness representations may be generalized, for example so that the word 'cancer' evokes vivid emotional representations of the familiar illness, even when one rationalizes that types of cancers vary, as the focus group data of this study suggested. As a result, lay illness representations and illness categories may be different to those of professionals.

The qualitative results showed that categories of 'multifactorial diseases' and 'heritable diseases' that are somewhat clear-cut for professionals, might be less so for lay people. While professionals may use categories such as 'actionable heritable diseases', 'non-actionable heritable diseases', ' carrier status for recessive heritable diseases', and 'multifactorial diseases', lay people could be more in terms with categories such as 'somatic diseases' and 'psychiatric diseases', or 'cancer' and 'heart disease'. These perspectives are not contradictory, but they provide different points of views for interpreting meanings of genetic risk information. Experts make a clear distinction between polygenic risk scores for multifactorial diseases and single variants indicating high risks for heritable diseases, but lay people may approach genetic risk information primarily from the point of view of disease type, instead of magnitude of risk or mode of inheritance (Bacon et al., 2015).

Differences in professional and lay ways of categorizing diseases can be understood from the perspective of the Common Sense Model of illness representations (Hagger & Orbell, 2003; Leventhal et al., 1980). Whereas health professionals may emphasize the *cause* and *control* dimensions since they focus on prevention and treatment of the illness, lay people may put more emphasis on, for example, the *consequences* dimension since they evaluate how living with the illness would be like as an experience. Also previous qualitative research has shown that even when lay and expert understandings of diseases match well, long-term consequences seem to be a more dominant aspect of lay illness representations compared to expert conceptualizations of diseases such as CVD and diabetes (Damman & Timmermans, 2012).

Consequences could also be related to personal identity (Viberg, Segerdahl, Hösterey Ugander, Hansson, & Langenskiöld, 2018), which is why potentially stigmatizing information could be threatening irrespective of the health implications. Focus group participants of this study considered communicating risks to younger people as more problematic, since they considered it could have a stronger impact on their social relations and life choices at that point. Similarly to focus group participants of this study,

genetic experts have pointed out that receipt of psychiatric genetic risk information could be more harmful than risks for somatic diseases (Kostick et al., 2018). A recent study among psychiatric genetic researchers (Kostick et al., 2018) shows that some experts view that knowledge of actionable psychiatric risks should be available for people, similarly as actionable somatic risk information. Still, experts hesitate how to balance between protecting psychiatric patients from distress, and not being too paternalistic. As a consequence, currently only a minority of experts consistently communicate psychiatric genetic risks to patients (Kostick et al., 2018). The current study adds to this discussion the point of view that responsibilities for managing psychiatric and somatic risks may be seen differently allocated, and this could contribute to potential distress of receiving risk information for different types of diseases. Since participants perceived that access to care is better for somatic diseases compared to psychiatric diseases, receiving psychiatric risk information was seen to impose stronger responsibility for the individual to manage such risks. Hence, psychiatric risk information seemed more distressing also because how psychiatric treatment is organised, not only because of the nature of illness per se.

The dimension of illness *identity* as proposed by the CSM (Leventhal et al., 1980) may be useful for understanding processing of risk information. Identity refers to the label of the illness and its characteristic symptoms (Hagger & Orbell, 2003); an illness with a clear label and symptoms that make sense is perceived as a more coherent whole than an an illness without clear symptoms. In a previous quantitative assessment among families with LS or BRCA mutations predisposing to breast and ovarian cancers, perception that the illness is ambiguous and does not make sense as a whole was associated with higher distress six months after predictive genetic testing for cancer (van Oostrom et al., 2007b). In contrast, other studies have linked coherent illness identity with higher distress (Hagger & Orbell, 2003), but this could be because illness identity is often measured as presence of symptoms. In the current study, perceived ambiguity of LQTS provoked some distress. On the other hand, FH tended to be paralleled with high cholesterol and hence as a risk factor, not as an illness in itself, and therefore less threatening, althout it is a serious condition if untreated (Youngblom et al., 1993). Cancer was perceived as a clear entity but still distressing because of severe consequences. More research is needed on how coherence of illness identity interacts with other dimensions of illness represenations, particularly in contexts of genetic risks and variants of unknown significance. Similarly as a disease, also a certain risk variant may have a clear identity and implications, or a vague identity and unclear implications, which could induce more distress over the uncertainty (Solomon et al., 2017).

Focus group data of this study showed that dimensions of illness representations could be applied not only to the *illness* but also to the *risk* of illness. The data showed that knowledge of risk extends the perceived *timeline* of the disease. The start of the illness could be at the time of first symptoms or

diagnosis, but receiving risk information seemed to be perceived as the starting point for living with the potential illness. Receiving genetic risk information will have *consequences* for one's life even before illness occurs. Potential worry and preventive medications or screenings were perceived to potentially affect quality of life as a whole. In a way, recipients of risk information become 'pre-patients'. Lay people may not always clearly distinguish being at risk from being ill (Damman & Timmermans, 2012). Instead, being 'at risk' can be experienced as a liminal state between being healthy and being ill (Scott, Prior, Wood, & Gray, 2005).

Understanding implications of being 'at risk' sheds light on why people might decline genetic testing even when it would be 'rational' from the perspective of disease prevention. For example, representations of what it means to be 'at risk' could contribute to choosing not to proceed with or procrastinating with genetic testing for heritable diseases such as Lynch syndrome, which has efficient preventive possibilities (Jarvinen et al., 2009). Previous studies have raised questions why a considerable proportion of individuals who have Lynch syndrome in their family have not proceeded with genetic testing (Aktan-Collan et al., 2011; Seppälä, Pylvänäinen, & Mecklin, 2017). Whereas from the expert perspective it would be sensible to get tested for Lynch syndrome and attend surveillance if needes, from the lay perspective the step of taking the test may carry more meaning for one's identity: a shift from being a 'healthy person' to being 'at risk'.

Psychological implications of being 'at risk' are also important from the perspective of resources of healthcare systems. Focus group participants of the current study were concerned whether there would be preventive surveillance and treatment available, if they were to be defined as 'at risk'. Previous qualitative studies have even reported that people may be disappointed if genetic testing reveals they are *not* at high risk, because they may still perceive high risk based on their family history, but then they will not have access to services and may feel abandoned (Scott et al., 2005). If people are informed about their health risks, they may seek reassurance from surveillance (Parsons, Beale, Bennett, Jones, & Lycett, 2000). These perspectives need to be considered when formulating new practices in the field of genomics. If people are told they are 'at risk' they may perceive they are not healthy. To support public trust towards the healthcare and research, attention needs to be paid to resources for counselling and preventive treatment when communicating genetic risks.

Overall, the qualitative results of this study highlight that it is important to consider the wider context of the healthcare system in different countries when forming practices of reporting genetic risks. Participants of the qualitative study worried about whether preventive treatment would be available after receipt of secondary findings (sub-study III). These findings support previous research results that highlight the importance of treatment plans (Daack-Hirsch et al., 2013) and timely access to re-testing (Haukkala et al., 2013).

The worry for clear treatment paths of the current qualitative inquiry may be partly explained by the current context of Finnish public healthcare. Public perception of efficiency and equality of healthcare in Finland are among the highest in Europe (Schneider & Popic, 2018), but a large reform of the public healthcare and social welfare services has been under preparation for several years. The reform was only once explicitly mentioned during the focus groups, but the complexity and uncertainties of this reform may have contributed to focus group participants' worry about how preventive treatment would be organised, and whether access to it would be equal for everyone. Even though ethical principles of informed consent, promoting well-being and avoiding harm apply similarly everywhere, it needs to be acknowledged that practices of communicating genetic risks happen within existing relationships between individuals and institutions. These relationships form the context to risk communication practices. Trust towards healthcare and research is essential to achieve successful practices, but carelessly formed practices could also damage public trust towards healthcare and scientific research. Ethical discussion around communicating genetic risks needs not only to go on around consent practices but also on practices of referral to preventive treatment for individuals and families.

8.3 METHODOLOGICAL CONSIDERATIONS

This study combined quantitative and qualitative methods to gain overall understanding of risk perceptions and a nuanced understanding of how people process new risk information. The different approaches complemented each other (Johnson et al., 2007). Since the quantitative and qualitative sub-studies focused on somewhat different questions and diseases, it was not plausible to triangulate the quantitative and qualitative data during the analysis process. However, variation of methods came useful when interpreting the study results. Results of the qualitative studies provided additional insight into the more detailed ways in which people evaluate their personal risks for various types of diseases. The study was conducted in a Nordic society with a public healthcare system and a highly educated population (Official Statistics of Finland, 2017), and the results may not be applicable in societies that greatly differ in these respects.

The quantitative studies used comprehensive Finnish population based survey and health examination data and allowed both cross-sectional and longitudinal assessments. The data was large enough for examining interactive effects of family history and other factors in relation to perceived risk. However, participants of FINRISK studies (sub-studies I and II) have a lower mortality rate compared to non-participants (Harald, Salomaa, Jousilahti, Koskinen, & Vartiainen, 2007), and participants of the qualitative studies were self-selected. Hence, the study was likely to include people who are healthier

and more interested in health compared to the population average. In addition to this, the qualitative studies included few males, who may hold lower risk perceptions and process risk information differently compared to females (Kahan et al., 2007). Despite these limitations, the quantitative data allowed comparing different risk groups, and the qualitative study sample was diverse in terms of age, professions, and educational level.

A strength of this study was that it was able to include both cross-sectional and longitudinal data on risk perception and risk factors, and thus provided the possibility to examine whether risk perception rather follows risk indicators or predicts health behaviour changes (Weinstein & Nicolich, 1993). The cross-sectional data showed that risk perceptions and risk factors are related to each other, and longitudinal data showed that perceived risk of chronic diseases did not lead to health promoting changes in behavioural or physiological risk indicators. However, it should be noted that conditioned risk perceptions (Brewer et al., 2007) were not assessed in this study. The questionnaires did not ask whether participants based their risk perceptions according to their current health behaviours, or whether they took into account their possible intentions to change their health behaviour for better or for worse. The measure of perceived risk captured perceived likelihood of developing the disease in question during one's lifetime; perceived severity of disease was not assessed. The qualitative data showed that perceptions of disease severity did shape reactions to risk information and coping intentions. Including perceived severity of disease in quantitative studies could help to gain a more nuanced understanding of risk perception and health behaviour. Weakness of some of the non-validated self-reported measures used in sub-study II – physical activity, self-efficacy, and outcome beliefs – may have resulted in conservative study results. Still, the study sample was large enough for using the statistical method structural equation modelling, which strengthened the study, as it helps to take into account covariation of multiple predictors and the effect of measurement error, and the method allows multiple-group analyses (Lomax & Schumacker, 2004).

The qualitative inquiry could be criticised for the use of hypothetical scenarios, since people's evaluations in imagined situations may not match how they think and act in a real life situation (Persky, Kaphingst, Condit, & McBride, 2007). However, with this approach it was possible to interview the participants immediately after they hypothetically had received secondary findings. In the midst of the possible shock of real life secondary findings, it might not be possible to conduct similar group interviews. Using this methodology it was possible to capture immediate perspectives on the matter, which might not come up if interviews were conducted later, after people have had time to adjust to the situation. Individual interviews would have allowed gaining deeper understanding of how individuals process risk information in relation to their personal life. However, a strength of the focus group approach was that it revealed some ways in which the social context affected how worries about genetic risks are expressed (Hollander, 2004). Shock and worry tended

to be expressed in a more straightforward manner in the private, individual written accounts, whereas during focus group discussions, participants made efforts to appear rational and not too prone to worry, as that was seen as an undesirable characteristic. Worries may still be more easily expressed in female dominant groups (Hollander, 2004). Perspectives on risk information may differ by gender (Kahan et al., 2007), but few males took part in the qualitative inquiry. Similarly, social norms could shape how people respond to research inquiries on reactions to secondary findings, or how they express worries during clinical encounters. Those with negative reactions to genetic results might not directly express this, if such reactions are perceived socially undesirable.

The number of study participants in the qualitative studies was quite small, and individual perspectives on the topic of secondary findings varied greatly. These limited the possibility to compare reactions to different types of secondary findings, which the method of empathy-based stories (Eskola, 1998) could be used for. Any comparisons between reactions to different types of secondary findings need to be interpreted as tentative, also because the vignettes used were parallel in structure but varied slightly in terms of content and length. We aimed to make the vignette letters as realistic as possible and not too frightening, and this is why numerical risk estimates or severe consequenses of the diseases were not described in the vignettes but were only discussed later in the focus groups. The familial hypercholesterolemia letter provided somewhat more detailed description, to convey that the condition is different from mildly elevated cholesterol. Our study results supported these choices, as the participants still thought the cancer letters were considerably more distressing.

In each focus group, one cancer syndrome and one cardiovascular condition were discussed simultaneously. This clearly encouraged comparisons between these broad disease categories, whereas the study design provided less possibilities to explore perspectives on different types of cancer syndromes or different types of cardiovascular conditions. A previous study simultaneously examined perspectives on genetic testing among families with Lynch syndrome and families with BRCA 1/2 mutations that are linked to breast and ovarian cancer (van Oostrom et al., 2007a). They found that people among families with Lynch syndrome had a more positive outlook on hereditary cancer, whereas people among families with BRCA had more distress and more passive coping styles. In the current study, more nuanced perspectives on various types of cancers or cardiovascular conditions might have been observed, had these been discussed during the same focus group sessions.

8.4 IMPLICATIONS FOR FUTURE RESEARCH AND PRACTICE

Increased use of genomic sequencing is likely to have many implications for healthcare. Whereas many other risk indicators, such as health behaviour, body weight, or biomarkers can be modified through health behaviour changes or medications, genetic predispositions are stable, although their interpretations may change as knowledge of genomics accumulates. However, genomics aim to identify people at high disease risks more accurately than before, so that lifestyle interventions and preventive treatments may be targeted more efficiently. In addition to possibility to calculate polygenic risks scores for multifactorial diseases and detecting single high-risk variants, genome sequencing may reveal pharmacogenetic findings that indicate sensitivities to medicines, or carrier status of recessive heritable diseases. Considerable proportions of survey respondents (Haukkala et al., 2018; Vermeulen, Henneman, van El, & Cornel, 2013) express interest in various types of genomic information that could be used in disease prevention.

The qualitative results of this study suggest that people may approach the topic of genetic risk information primarily from the point of view of familiar illnesses, and may not clearly distinguish between, for example, multifactorial and heritable forms of diseases. Future studies need to be designed to examine how people process qualitatively different types of genetic risk information, including polygenic risk scores, high risk single variants, and carrier status, and how the nature of disease interacts with this processing. The qualitative results of this study showed that people were particularly worried about risks for their children. Carrier status for recessive heritable diseases and dominant high risk variants are treated differently in genomic practices, but from the point of view of worry for children, these types of risk information may share many meanings for lay people.

Both qualitative and quantitative results of this study indicate that lay perspectives on hereditary risk information vary according to disease type. In the quantitative assessment of study I, the association of family history and perceived risk was weaker for depression compared to somatic diseases. Further research is needed to conclude whether this is because people are less aware of hereditary predisposition for depression or psychiatric disorders more generally, or whether they stress environmental factors or current signs of psychiatric symptoms more when considering psychiatric risks. Unexpectedly, the inductive thematic analysis of the qualitative data of this study revealed that people may perceive psychiatric genetic risk information more distressing compared to genetic risk information for somatic diseases. At the same time, individuals were seen as responsible to monitor early psychiatric symptoms and find treatment on time. More research is needed on how perceptions of heritability of different types of diseases contribute to perceptions of responsibilities for managing risks and illness. Future studies need to explore more specifically, how lay people evaluate hereditary risks for

psychiatric diseases, and whether these evaluations translate into how they manage such risks; for example, whether perceptions of hereditary psychiatric risks contribute to treatment seeking.

Health behaviour theories of risk perception (Becker, 1974; Schwarzer, 2008) focus on individual risks. Future research around genetic risks needs to explore ways to incorporate the family perspective into risk perception theories, to understand how, for example, perceptions of risks for children may contribute to preventive actions. Furthermore, research on illness representations needs to explore how representations of being 'at risk' for hereditary illnesses are integrated into illness representations, and whether these representations contribute to preventive actions.

The qualitative results of this study showed that lay perspectives on receiving secondary findings from genome sequencing depend not only on the type of secondary findings but also on how counselling, surveillance and treatment for different conditions are organised. Practices of reporting genetic risks need to be carefully evaluated in contexts of different healthcare systems. When reporting genetic risks, attention should be paid not only to consent and reporting practices but also the practical paths through which people get access to counselling and relevant preventive treatment. This has implications for, among others, biobanks who report genetic risks back to biobank participants. Results of the current study show that it is not advisable to simply return risk information, but this needs to be combined with practical advice on where individuals may look for further reliable information, preventive treatment, and counselling for how to communicate this information within the family. Individuals should not be left on their own to make sense of genetic risk information without a possibility for expert support. Furthermore, it needs to be acknowledged that individual preferences and life situations may change in varied ways between the time of consent and the time when risks are reported to them. These lay perspectives need to be taken into account in guidelines, regulations and practices of reporting genetic risks.

9 CONCLUSIONS

Despite optimistic bias, risk perceptions of common diseases reflect actual risk factors such as family history, and behavioural and physiological risk factors. Family history contributes to perceived risk of diabetes, CVD, cancer, and depression independently of sociodemographics, health behaviour, body weight, and current depressive symptoms. Perceived risk of disease or biomarker feedback alone, however, are unlikely to predict health promoting changes in physical activity, body weight, or blood sugar. Interventions need to target risk perceptions together with other social cognitive factors, such as self-efficacy. This needs to be kept in mind when developing more and more individualized forms of risk feedback, such as polygenic risk score information concerning multifactorial diseases.

Lay illness representations need to be taken into account in risk communication, as previous knowledge of diseases shapes how people process new risk information. When communicating genetic risks, it should be noted that lay people may not distinguish different types of diseases, for example heritable and multifactorial diseases, similarly as professionals do. This needs to be kept in mind also when formulating categories from which to choose from when consenting to secondary findings, to provide people with categories that they find useful and helpful for decision making. When reporting secondary findings from genome sequencing, people may expect timely access to counselling support and preventive treatment. In addition to formulating acceptable consent practices for receipt of secondary findings, preventive treatment paths for individuals and families need to be planned and communicated appropriately.

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